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EXTRAMEDULLARY ERYTHROCYTOPOIESIS IN MAN

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Extramedullary hemopoiesis is a common phenomenon associated with certain anemias and leukemias. The condition is generally interpreted as compensatory for a hypofunctional bone marrow. Uncertainty concerns especially the source of the proerythrocyte in the metaplastic tissues. It is the purpose of this study to describe in detail two cases of extensive erythroid metaplasia, and to attempt an interpretation of the special conditions in the light of the data revealed by the evolutionary history of blood-forming tissues. Such interpretations must recognize the fundamental importance of the spleen in the production of the red cells and the potential erythrocytogenic capacity of the lymphocytes.

The two cases of erythroid metaplasia under consideration are complementary in that one shows extensive involvement of lymph nodes following damage to the bone marrow and spleen while the other shows very active splenic hemocytopoiesis associated with a considerable replacement of lymph nodes and bone marrow by metastatic adenocarcinoma from the prostate.

CASE 1[1]

CLINICAL HISTORY

A white woman of about 40 years was admitted to the University Hospital on June 23, 1924. She complained of weakness and of a mass in the left side. She first noticed the mass about one year earlier. It had progressively grown larger, particularly since January, 1924. She presented a perplexing condition indicative of leukemia, but whether this was myelocytic, lymphatic or mixed was uncertain. She grew rapidly worse. The very large spleen receded after treatment with radium on June 28, but the blood picture did not improve. The exposure to radium of 3,200 mg.-hours led to a rather violent reaction. She died unexpectedly on July 8, 1924.

On admission the erythrocytes numbered 1,050,000 per cubic millimeter; on July 4, six days after treatment with radium, 886,000. On admission, the hemoglobin (Dare) was 15 per cent. The bleeding time was twenty-six minutes; the clotting time, six minutes. The platelets numbered 39,000. The leukocyte count was 70,000; two days after treatment with radium, 9,200; four days later, 3,200. The differential count on admission was: neutrophils, 10.6 per cent; small lymphocytes,

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1. The materials studied in this case are on file with the Lymphatic Tumor Registry as Accession No. 32825. A brief report was published in collaboration with Dr. H. T. Marshall under the title, "Metaplastic Development of Erythrocytes in Lymph Nodes," Anat. Rec. **29**:363, 1925.

83.3 per cent; large lymphocytes, 3.7 per cent; eosinophils, 0.3 per cent; mast cells, 0.1 per cent; transitionals, none; neutrophilic myelocytes, 1.4 per cent; eosinophilic myelocytes, 0.5 per cent; basophilic myelocytes, 0.1 per cent. Two normoblasts and 1 microblast were seen.

AUTOPSY REPORT

The condition of the lungs suggested early pneumonia. The peribronchial lymph nodes were large, moist, congested and ecchymotic, and soft. The immediate cause of death was probably bronchopneumonia of hemorrhagic type. Accompanying the pneumonia was a lymphadenitis of hemorrhagic type along the bronchial nodes. The spleen weighed 690 Gm.; its length was 17.5 cm.; its breadth about one half the length. The bone marrow of the femur was hemorrhagic and rather watery in texture, with small, spongy bits of tissue in the watery red background. There was no white marrow or fat. The bone marrow of the ribs and vertebrae was of similar character. The lymph nodes of the neck, axillae, mesentery and inguinal region were soft, somewhat enlarged and red or pink.

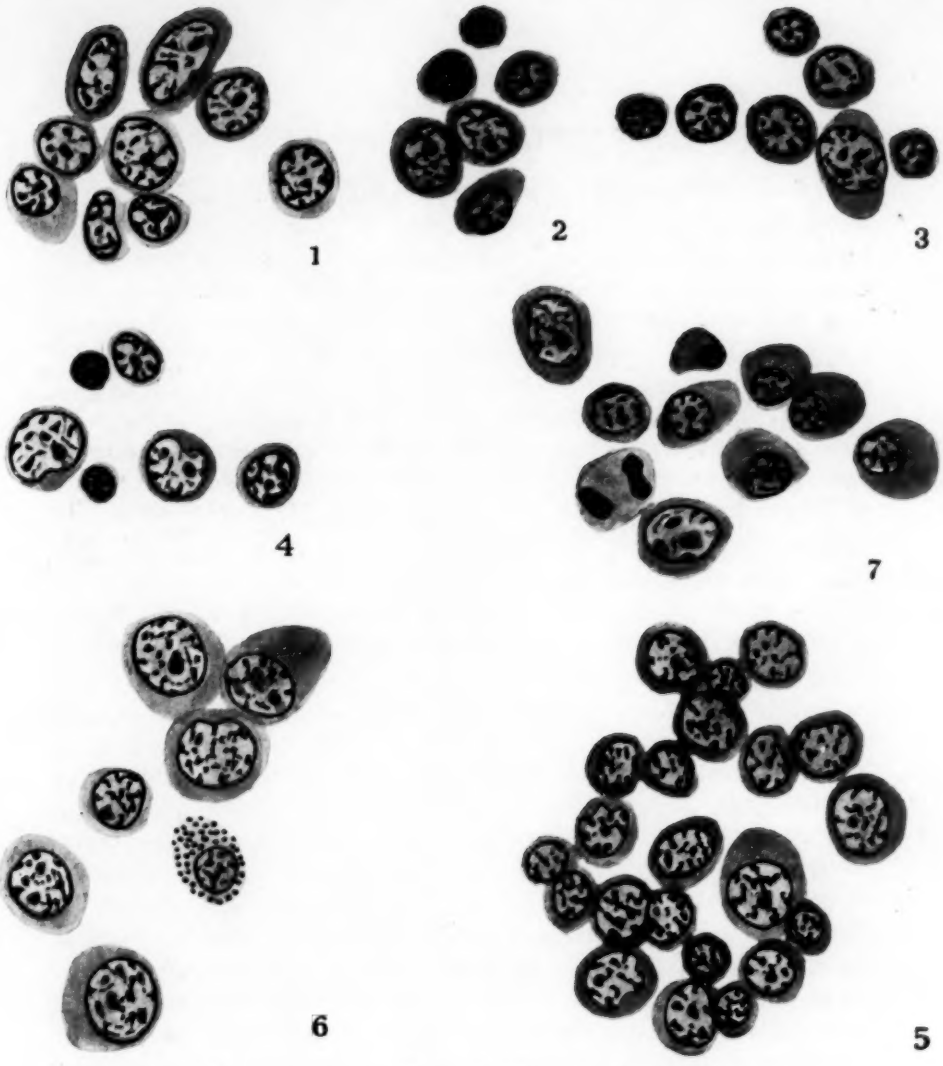
HEMOPOIESIS

Marrow.—Smears were made from a rib, a femur and a vertebra, and stained with Wright's stain. The small lymphocytes predominated; a considerable number of lymphocytes of intermediate size also occurred. Typical hemocytoblasts, erythroblasts and normoblasts were abundant. Only one megakaryocyte was seen. Granulocytes, both neutrophilic and eosinophilic, were rare. The absence of mitoses seems to indicate abeyance of local histogenetic activity.

Sections of femoral marrow, fixed in Helly's fluid [1a] and stained with either hematoxylin and eosin or the eosin-azure combination of Giemsa, gave the appearance of lymphoid metaplasia. Approximately half of a transverse section consisted of moderately dense lymphoid tissue, with a suggestion of several nodules. Small lymphocytes greatly predominated. A few large lymphocytes (hemocytoblasts) and numerous transitionals in the form of medium-sized lymphoid hemoblasts occurred (fig. 5). Many of the small lymphocytes were in stages of degeneration, as indicated by an extensive karyorrhexis. In the other half of the section definitive red blood corpuscles predominated; this region also contained widely scattered small and intermediate-sized lymphocytes and hemocytoblasts (fig. 6), erythrocytes at various stages of maturation (fig. 7), megakaryocytes and a few macrophages with erythrocyte débris. The area of junction between the compact lymphoid tissue and the loose erythroid tissue had an intermediate histologic structure. There was no indication of erythrocytogenic activity on the part of the endothelium.

1a. The formula for Helly's fluid is as follows:

Potassium bichromate	2.5 Gm.
Sodium sulphate	1.0 Gm.
Mercuric chloride	5.0 Gm.
Distilled water	100.0 Cc.
Dilute formaldehyde solution	5.0 Cc.



EXPLANATION OF PLATE 1 (CASE 1, LEUKEMIA)

All of the drawings were made at a magnification of 1,350 diameters, from sections of tissues fixed in Helly's fluid, the sections having been stained with hematoxylin and eosin.

Fig. 1.—Group of cells from a splenic nodule. Included among them are small and large lymphoid hemoblasts and one erythroblast (below, at left). The large lymphoid hemoblast is the equivalent of the hemocytoblast; the small, of the lymphocyte.

Fig. 2.—Group of cells from splenic pulp. Included among them are two lymphoid hemoblasts, three erythroblasts and one normoblast.

Fig. 3.—Group of cells from the periphery of a nodule of a lymph node, including one large and six smaller lymphoid hemoblasts.

Fig. 4.—Group of cells from a sinus of a lymph node, including a large and two smaller lymphoid hemoblasts, an erythroblast and two normoblasts.

Fig. 5.—Group of lymphoid hemoblasts of various sizes from bone marrow. This region resembles compact lymphoid tissue.

Fig. 6.—Group of large lymphoid hemoblasts (hemocytoblasts) from a less dense area of bone marrow. The group includes one eosinophil. This area includes many erythroplastids and a few megakaryocytes.

Fig. 7.—Group of cells from a region intermediate between those of figures 5 and 6, including two hemocytoblasts, a number of erythroblasts (one in mitosis) and one normoblast.

Spleen.—Different regions of the spleen differed histologically. The difference inhered in relative abundance of lymphocytes and stroma. Over large areas, in the aggregate apparently through the greater volume, lymphocytes were almost entirely lacking. Here the stroma was very prominent, and the lining of the partially collapsed sinuses was composed of closely spaced rounded cells giving a false appearance of exfoliation into the lumen. There were, however, no areas of hyalinization. In other areas lymphocytes were fairly abundant, including both large (hemocytoblasts) and small varieties, the latter greatly in excess. Between these areas in which conditions were extreme there were areas of intermediate lymphocyte content (figs. 1 and 2). Occasional macrophages, laden with red cells at various stages of differentiation, including a lymphocyte or two, were to be found. Megakaryocytes were absent. Monocytes occurred sparingly. Nucleated red cells and granulocytes were relatively rare. The most abundant granulocyte was a spheronuclear basophil.

Lymph Nodes.—The lymph nodes were uniformly enlarged. The microscopic study included several each from the neck, axilla and groin. This tissue was fixed in Helly's mixture of Zenker solution and diluted formaldehyde solution, and was stained either with the eosin-azure combination of Giemsa or with hematoxylin and eosin. The most characteristic feature of the lymph nodes was an almost complete obliteration of the demarcation between the cortex and the medulla. The parenchyma consisted generally of a uniformly compact mass of small and medium-sized lymphocytes (fig. 3), resembling somewhat splenic pulp. Occasional more compact masses of small lymphocytes suggested a previous nodule. Such nodules generally had light-staining centers of connective tissue with evidence of beginning necrosis and hyalinization. Large lymphocytes (hemocytoblasts) were also abundant; a few were in mitosis. Mingled with the lymphocytes were large numbers of red cells at all stages of differentiation (fig. 4). Cells transitional between hemocytoblasts and normoblasts were present in large numbers. There was no evidence of endothelial activity in the formation of hemocytoblasts. Megakaryocytes were lacking. Occasional macrophages with erythrocyte débris occurred. Granulocytes were rare, basophils predominating.

The arterioles were generally empty, their walls contracted and relatively thick. The venules were generally engorged with lymphocytes and differentiating erythrocytes. The lymph nodes resembled splenic pulp, with large, apparently fenestrated sinusoid spaces. The differentiating red cells occurred both in these "pulp sinuses" and extravascularly among the lymphocytes. The appearance suggested an extravascular differentiation of red cells from lymphocytes. Mitoses occurred only in the large lymphocytes.

COMMENT

An attempt at interpretation of the histology of the marrow, spleen and lymph nodes must take into account the cellular content of the peripheral blood. The outstanding differential feature was the drop in the number of leukocytes from 70,000 to 3,200 within six days after the treatement with radium. Neither the total red cell count of approximately 1,000,000, nor the relative proportions of the white cells were markedly affected by the radium treatment. The greatest difference relates to the small lymphocytes; these suffered a decrease in number, leaving a relative increase in the number of the neutrophilic granulocytes. Platelets were relatively rare, and eosinophilic and basophilic granulocytes were practically absent. Nucleated red cells were very scarce, one differential count revealing only 2 normoblasts. Only the granulocytes of these blood smears gave a positive oxydase reaction; the mononuclear leukocytes were uniformly negative.

I am not especially concerned here with an effort to classify this case of leukemia, whether lymphatic, myelogenous or "mixed"; it seems to conform most closely to the case described by Fineman [2] in which the condition was designated "microlymphoidocytic leukemia." Nor does it seem desirable here to review again the extensive literature dealing with the question of single, dual or multiple sources of "myelogenous" cells in leukemia. This literature has been very thoroughly reviewed by Logefeil.[3] I am concerned primarily with the fact that under certain pathologic conditions the lymph nodes may partially compensate functionally for a morbid bone marrow or spleen, and with the evidence that lymphocytes may differentiate into erythrocytes, and with the implications of these data with respect to the significance of the lymphocytes in normal hemocytopoiesis.

Much of the recent work on leukemias leads to the conclusion that under the conditions prevailing in this type of disease the lymphocytes of the lymph nodes may differentiate into "myeloid cells." Thus Citron,[4] in his discussion of a case of "micromyeloblastic leukemia," stated his belief that "in some cases a direct autocellular change of lymphatic follicular lymphocytes into myeloid cells may take place" in both the spleen and lymph nodes. Fineman [2] in a case of microlymphoidocytic leukemia noted the abundance of forms transitional between lymphocytes and hemoblasts ("atypical cells") both in the peripheral blood and in the lymph nodes, but was unable to determine "whether the lymphocyte is the mother cell of our atypical cell or vice versa." Logefeil [3] found evidence in a case of "mixed leukemia" of a "direct transition from

2. Fineman, S.: Arch. Int. Med. **29**:168, 1922.
3. Logefeil, R. C.: Arch. Int. Med. **33**:659, 1924.
4. Citron, J.: Folia haemat. **20**:1, 1915.

lymphocytes to myelocytes, without going through the stage of the stem cell" (hemocytoblast). He noted also evidence of a local development of myelocytes from lymphocytes in the areas of leukemic infiltration in the pancreas, kidneys and lungs. Furthermore, in both the lymph nodes and the spleen he found "immature" lymphocytes and myelocytes diffusely arranged without evidence of segregation. He stated that "many of the eosinophils, both immature and adult, had nuclei identical with adjacent lymphocytes." He quoted Turk (1908) as having reported the presence of many nucleated red cells in the lymph nodes in a case of "mixed leukemia." But no definite statement appears as to whether these cells were belived to be the result of infiltration or of local differentiation. Finally, Downey [5] stated that "under pathological and experimental conditions which cause myeloid metaplasia the derivation of myeloid cells from lymphocytes without the intervention of the myeloblast may be an extensive process." He admitted further that the blood in lymphatic leukemia may show all transitional forms from the "myeloblast" (hemocytoblast) to the ordinary lymphocyte, without, however, committing himself as to which cell is the progenitor.

In the group of the Amphibia the evidence seems conclusive that the lymphocyte may function as a mother cell of both erythrocytes and granular leukocytes (Jordan [6]). This case of leukemia has especial interest because it furnishes apparently confirmatory evidence with respect to man. Here the data seem to exclude the possibility that the very numerous nucleated red cells of the lymph nodes were transported from the bone marrow. The peripheral blood contained very few nucleated red cells. The very numerous normoblasts could, therefore, not have entered the lymph nodes from the blood stream. Moreover, nucleated red cells, while numerous in the marrow, were relatively fewer there than in the lymph nodes. The erythroplastids apparently had origin largely in the lymph nodes but to some extent in the spleen and the marrow. Numerous stages in the enucleation of the normoblasts also appeared in the lymph nodes, spleen and marrow.

The possibility, of course, remains that the small lymphocyte-like cells of the lymph nodes, which differentiated here into erythrocytes, were specific proerythroblasts whose ancestors early in the morbid condition found lodgment in the lymph nodes, there to develop the erythrocytopoietic "metaplasia" of the leukemia. This objection cannot be met with any definite or final statement. It can only be said that on the basis of the morphologic and tinctorial criteria here possible of application no difference can be detected between alleged distinct lymphocyte ancestors and erythrocyte ancestors. The lymphoid cells of the lymph

5. Downey, H.: Arch. Int. Med. **33**:301, 1924.

6. Jordan, H. E.: Am. J. Anat. **51**:215, 1932.

nodes and the marrow which constituted the erythrocyte precursors in this case have an identical appearance in stained sections.

Briefly sketched the case may be interpreted as follows: The dysfunction of the marrow, the primary cause of which remains unknown, resulting chiefly in a condition of severe anemia, stimulated a compensatory reversion of the spleen to its embryonic hemocytopoietic condition. Relatively intense proliferative activity or inability of sufficiently rapid differentiation of splenic polyvalent lymphocytes into erythrocytes (due possibly, at least in part, to a lack of favorable conditions for the development of hemoglobin) caused an accumulation of the lymphocyte red-cell ancestors, with a consequent enlargement of the spleen. Radium irradiation then destroyed large numbers of the splenic lymphocytes with a consequent decrease in the size of the spleen and the production of the histologic condition of large areas of lymphocyte-free stroma. Following this intentional destruction of the lymphocytes of the spleen, compensation was attempted on the part of the only other available potentially myeloid tissue, namely, the lymph nodes.

CASE 2

MATERIALS AND METHODS

The materials of this study included the spleen, bone marrow, lymph nodes and liver in a case of adenocarcinoma of the prostate. The tissues were fixed in Helly's fluid. Some of the sections were stained with hematoxylin and eosin; others, with the eosin-azure combination of Giemsa.

The patient died within two hours after admission to the University Hospital. Unfortunately no blood smears were secured. The clinical history is meager. The prostatic carcinoma had metastasized widely in lymph nodes, bone marrow, lungs, liver and kidneys. There were no tumor cells in the spleen. The mesenteric lymph nodes were greatly enlarged and almost completely replaced by tumor cells; in some nodes hardly a trace of lymphoid tissue persisted. The bone marrow showed extensive invasion. The tissues of primary interest in this connection were the liver, the spleen and the bone marrow.

CLINICAL HISTORY

The patient was admitted to the University Hospital at 5 p. m., complaining of shortness of breath and swelling of the feet and ankles of about ten days' duration. He had been in good health up until six or seven months prior to this, at which time he began to suffer with pain in the back and legs. He had no swelling of his feet and legs at that time. During the past two weeks he had had a troublesome cough that was productive of a purulent sputum. He had lost "a lot of weight" during the past year.

Physical examination revealed a well developed and well nourished white man about 63 years of age who was markedly dyspneic. The retinal vessels showed arteriosclerotic changes. Pyorrhea was present. The tonsils were chronically diseased. The respirations were rapid and shallow. There was dulness to percussion from the level of the fourth dorsal spine posteriorly to the base of the lung on the

left. The apex beat could be neither felt nor heard. The heart sounds were very distant but regular. The abdomen was distended. The edge of the liver extended about 3 fingerbreadths below the costal margin and was quite tender. The prostate was normal in size and regular in contour. There was an area of suspicious hardening in the left outer lobe. There was pitting edema of the feet and ankles and over the sacrum. On admission his temperature was 100.8 F. The pulse rate was 108. No examination of the blood was made. The patient died one hour and forty minutes after admission to the hospital. While he was in the hospital his chest was tapped and a bloody fluid obtained. Caffeine and epinephrine were given to him as emergency measures. A diagnosis of hypertensive heart disease with congestive failure was made. The bloody pleural effusion was explained as due probably to a pulmonary malignant process, possibly metastatic.

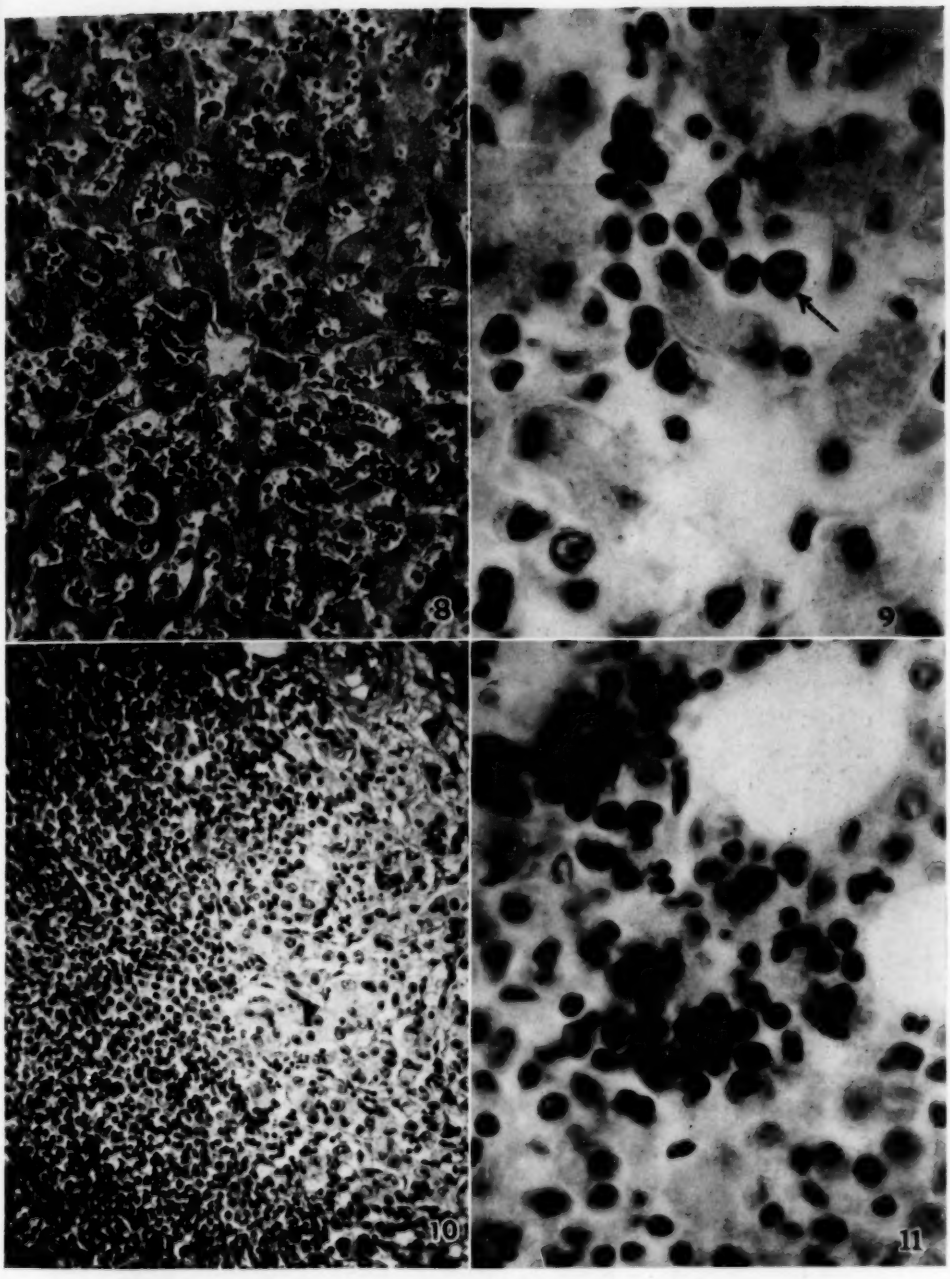
AUTOPSY REPORT

Since the data pertain largely to the metastasizing carcinoma, it seems unnecessary to include them here.

Anatomic Diagnosis.—Adenocarcinoma of the prostate, with metastases to pelvic, retroperitoneal, abdominal, axillary and inguinal lymph glands and to the liver, lungs, peritoneum, pleurae, adventitial layer of the pulmonary artery and bone marrow; extensive extramedullary formation of blood in the liver, spleen and perirenal fat; serosanguineous pleural and pericardial effusions; thrombosis of small branches of the pulmonary arteries; infarction of the spleen; fibrosis of the pancreas with hypertrophy of the islands of Langerhans; generalized arteriosclerosis; scarring of the heart muscle and kidneys; Mönckeberg's sclerosis of peripheral arteries; slight cardiac hypertrophy (left ventricle); nephrolithiasis with hemorrhage into the renal pelves; chronic cholelithiasis and appendicitis; abdominal adhesions; atrophy of the testes.

HEMOPOIESIS

Liver.—The striking feature of the liver was the condition of the intralobular capilliform sinusoids. Formation of red cells was very active within the sinusoids. In many regions the sinusoids were almost completely filled with collections of cells including all stages of erythrocytogenesis (fig. 8). The most conspicuous cell was the relatively large hemocytoblast, with a large, vesicular, finely granular nucleus, one or several nucleoli and basophilic cytoplasm (figs. 9 and 22). These cells occurred in large numbers; they appeared identical with those of similar groups in the bone marrow and spleen; many were in mitosis. No evidence of a local origin appeared; the reticulum cells and endothelium were hemopoietically inactive. The Kupffer cells of the sinuses were phagocytically active; many of the cells contained ingested erythroblasts. The source of origin of these groups of hemocytoblasts and maturing cells within the hepatic sinusoids was obviously the spleen; the hemocytoblasts were swept to the liver via the splenic vein-portal vein route, and continued maturation under the favorable erythrocytopoietic condition of the relatively stagnant venous blood of the sinusoids.



EXPLANATION OF PLATE 2 (CASE 2, ADENOCARCINOMA OF PROSTATE)

Fig. 8.—Section of a hepatic lobule. The central vein is empty. The capilliform sinusoids contain groups of hemocytoblasts and maturing erythrocytes. Helly fixation; hematoxylin and eosin stain; × 180.

Fig. 9.—Area of hepatic tissue showing a capilliform sinusoid filled with blood cells, including one hemocytoblast (indicated by arrow) and a number of erythroblasts and normoblasts; × 800.

Fig. 10.—Area of femoral marrow, showing large mass of tumor cells at the right; × 180. The tumor-free marrow is predominantly granulocytopoietic.

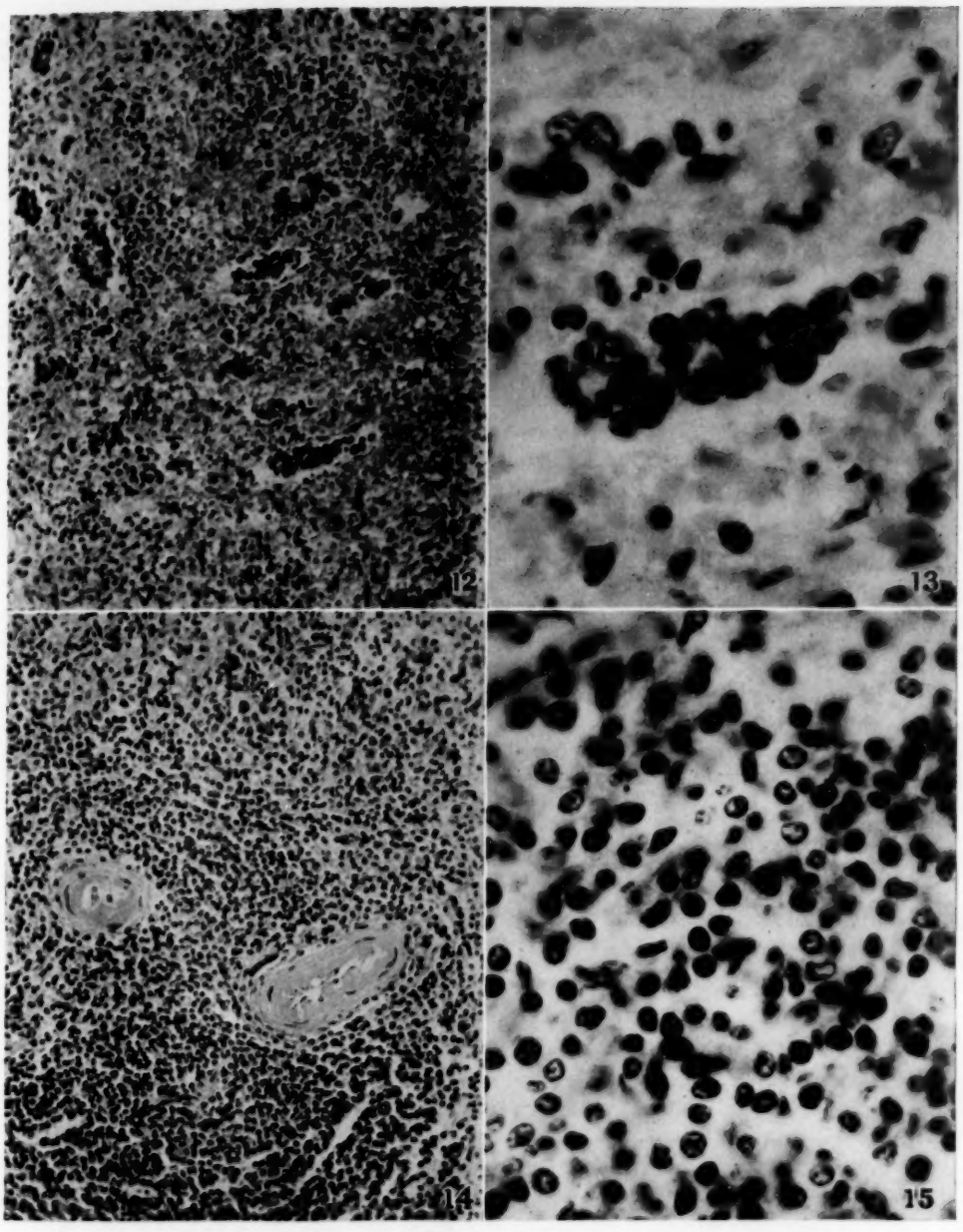
Fig. 11.—Relatively normal area of the femoral marrow of the section reproduced in figure 10, showing two groups of maturing erythrocytes, including a few hemocytoblasts; × 800.

In certain regions the periportal area also showed hemocytopoietic tissue. The cells were mostly of the small lymphocyte type. These were apparently of local origin. The areas contained typical large hemocytoblasts, normoblasts and many cells of intermediate stages between small lymphocytes and hemocytoblasts.

Bone Marrow.—The erythrocytopoietic tissue of the bone marrow was greatly restricted through invasion by the tumor (fig. 10). Only femoral marrow was removed at autopsy. However, the specimen had a length of approximately 6 cm.; all of this was extensively invaded by tumor cells. In view of the conditions in the femur it seems legitimate to assume that bone metastasis was widespread. In a typical section of the femoral marrow there remained centrally a core of apparently normal tissue. Both granulocytopoiesis and erythrocytopoiesis were active. The groups of hemocytoblasts and maturing red cells here were identical with those in the hepatic sinusoids (fig. 20). In general, however, the groups were smaller. These groups occurred in sinuses, distinct from the granulocytopoietic areas (fig. 11). Peripherally, in those regions free from metastasis, hemopoiesis was almost exclusively of the granular type. The appearance of the tumor-free marrow as a whole was one of very active granulocytopoiesis and meager erythrocytopoiesis. There was no evidence of local endothelial derivation of stem cells.

Spleen.—The spleen was more than twice its normal size. It measured 17 by 10.5 by 5 cm., and weighed 510 Gm. It was extremely active in the formation of red cells. It contained no tumor cells. Eosinophilic and neutrophilic granulocytes were rare and uniformly of definitive type; they were obviously not formed locally. In other respects the spleen looked like bone marrow (fig. 12) except for the small lymphoid (splenic) nodules (fig. 14); megakaryocytes were almost as numerous as in the femoral marrow. Basophils occurred in small numbers and were of local origin; they included all developmental stages from hemocytoblasts to definitive mast cells.

Primary interest concerns the origin of the very numerous hemocytoblasts, from which the red cells arose. The hemocytoblasts occurred in groups, with mingled maturing erythrocytes as in the liver and the bone marrow (figs. 13, 17, 18 and 19). Concerning the origin of the hemocytoblasts two possibilities are presented: (1) they may have been carried here from the marrow; (2) they may have arisen from the splenic parenchyma. The first possibility seems contradicted by the fact that the spleen contained very few granulocytes. If the hemocytoblasts and maturing erythrocytes of the splenic sinuses had been brought here from the marrow, it would be expected that granulocytes also were included, for they are abundant in the marrow. Accordingly, the hemo-



EXPLANATION OF PLATE 3 (CASE 2, ADENOCARCINOMA OF PROSTATE)

Fig. 12.—Area of splenic pulp; × 180. The sinuses are well filled with groups of hemocytoblasts and maturing red cells.

Fig. 13.—Splenic sinus (lowermost sinus in figure 12) showing a large group of blood cells; including hemocytoblasts, erythroblasts and normoblasts; × 800.

Fig. 14.—Splenic nodule, showing two arterioles; × 180. The area of transition between the nodule and the splenic pulp appears about midway between the arterioles and the upper edge of the figure. The predominating cell of the nodule is the small lymphocyte.

Fig. 15.—Area from the splenic nodule of figure 14; × 800. The periphery of the nodule shows in the upper portion of the figure. Small lymphocytes predominate. Cells transitional between small lymphocytes and hemocytoblasts are numerous. These nodules consist of cells in two stages of the lymphoid hemoblast: hemocytoblast and lymphocyte.

cytoblasts of the spleen presumably represented differentiation products of the local lymphocytes, derivatives of local reticular cells. There was no evidence that the local reticular or endothelial tissue functioned directly as a source of origin of the hemocytoblasts. It appears, then, that the spleen had reverted to a fetal condition as an erythrocytopoietic organ in compensation for the restriction of the normal erythrocytopoietic tissue in the marrow. Since the lymph nodes were almost entirely replaced by tumor tissue, the spleen must have compensated also in the production of additional lymphocytes. This obligatory, compensatory activity on the part of the spleen for both the lymph nodes and the red marrow presumably explains its great hypertrophy.

Lymph Nodes.—The majority of the lymph nodes, especially those of the mesenteric group, were greatly enlarged and except for an occasional trace of lymphoid tissue consisted of tumor cells; the appearance closely resembled that of the prostate.

In those lymph nodes in which the parenchyma had been only in part replaced by the tumor, the remaining lymphoid tissue was greatly altered; it closely resembled the spleen. The cortical nodules were confluent and only vaguely outlined; germinal centers were lacking. The sinuses were large and contained considerable blood. The predominating cell of the cortical region was the small lymphocyte. The medullary cords contained small groups of hemocytoblasts and adjacent maturing erythrocytes. There occurred also, especially along the corticomedullary boundary, large numbers of cells in transitional stages between small lymphocytes and hemocytoblasts. The erythrocytopoietic areas contained also numerous megakaryocytes. The tumor-free portion of the lymph nodes was converted into hemolymph gland tissue, the red cells arising from hemocytoblast derivatives of small lymphocytes.

Certain small lymph nodes as well as certain portions of the larger lymph nodes, both tumorous and tumor-free, contained considerable fat. Such tissue closely resembled red marrow. Formation of red cells was active, and megakaryocytes were abundant.

Most striking were the smaller tumor-free lymph nodes. These were genuine hemolymph nodes. There was no sharp demarcation between the cortex and the medulla. However, the cortical area showed a predominance of small lymphocytes. Certain slightly more compact regions probably marked the site of the original cortical nodules. The sinuses were well filled with blood. They contained also large numbers of hemocytoblasts and maturing erythrocytes. The parenchyma also contained hemocytoblasts and normoblasts as well as many cells in transitional stages between small lymphocytes and hemocytoblasts. Both sinuses and parenchyma contained also many megakaryocytes. No evidence appeared of phagocytic activity on the part of these cells. They

represented hypertrophied hemocytoblasts. The evidence from this material supports my earlier conclusion regarding the significance of hemolymph nodes (Jordan [7]): The evidence favors the interpretation in terms of a modified lymph node in which the small lymphocytes give rise to hemocytoblasts which differentiate into erythrocytes.

Fat Tissue.—The perirenal fat in the region of the hilus contained, adjacent to the renal papillae, numerous small well vascularized patches of erythrocytopoietic tissue. The predominating cell was the small lymphocyte. However, groups of hemocytoblasts and cells in all stages of the maturation into erythrocytes also occurred here. Some of these patches contained also, especially numerous peripherally, macrophages filled with yellowish-brown globules of variable size, presumably erythrocyte débris. It is possible that this hemocytopoietic tissue, like marrow, became active in destruction as well as in formation of red cells. Some of the patches contained also numerous megakaryocytes. Similar hemocytopoietic patches occurred in the perinodal fat in the sections of the lymph nodes and in the peripancreatic fat. The histologic conditions resembled closely those recently described by Blaisdell [8] in a retroperitoneal lipomatous tumor.

ERYTHROID METAPLASIA OF THE SPLEEN IN CASE 2

The genetic history of the splenic erythrocytes began with the lymphocytes of the nodules (malpighian follicles). The splenic nodules were small. They consisted almost exclusively of typical small lymphocytes (figs. 15 and 16). Peripherally there were sometimes considerable numbers of typical hemocytoblasts (fig. 19). Many of these were in mitosis. In the intermediate regions of the splenic nodules there occurred transitional stages between small lymphocytes and large hemocytoblasts. The splenic nodules lacked germinal centers (secondary nodules). This condition suggests the approach to a state of functional exhaustion. There was no proliferation of the small lymphocytes. However, hemocytoblasts both of the nodules and of the sinuses multiplied actively by mitosis.

The hemocytoblasts which originated from lymphocyte ancestors in the splenic nodules were carried into the splenic sinuses. Here they underwent maturation into red blood corpuscles (figs. 17 and 18). A certain number hypertrophied (fig. 21) and became ancestors of megakaryocytes. The megakaryocyte in later stages contained an extensively lobulated nucleus. There was no evidence that it arose as a fusion product of hemocytoblasts; the cell was mononucleated, the complex condition of the definitive nucleus representing a modified originally spheroid body. Nor was there any evidence that the splenic giant cell was capable of phagocytosis; it presumably had the same function here as in the bone marrow.

The dominating cell of the spleen was the hemocytoblast. In typical form it was a spheroid cell with a relatively large nucleus. It had a diameter of about 12 microns. In sections stained with eosin-azure the cytoplasm took a deep lilac color. The nucleus stained only lightly; it appeared vesicular; the delicate

7. Jordan, H. E.: Am. J. Anat. **38**:255, 1926.
8. Blaisdell, J. L.: Arch. Path. **16**:643, 1933.

reticulum was sparse, forming a wide-meshed net. The most conspicuous feature of the nucleus was the plasmosome (nucleolus). This body stained lightly in contrast with portions of the more chromatic nuclear reticulum. It was commonly of spheroid shape; but it sometimes was bilobed, or even of triangular or rectangular form in sections, with the edges continuous with the more deeply staining reticulum. Many hemocytoblasts contained two or three plasmosomes.

In the splenic nodules, as stated, occurred numerous cells that were transitional between the central typical small lymphocytes and the peripheral typical hemocytoblasts. The typical small lymphocyte had a diameter of about 8 microns. It had a spheric shape. It had relatively little cytoplasm; this stained light blue or lilac with eosin-azure. The spheric nucleus contained a coarse reticulum; the threads ended on the nuclear membrane in an expansion. This gave an appearance of peripheral arrangement of angular chromatin blocks. The reticulum frequently attached centrally to a larger angular chromatin mass. In lightly stained preparations this central chromatin nucleolus was seen to consist mainly of a spheric plasmosome. In the intermediate stages between the small lymphocyte and the hemocytoblast the cell attained an intermediate size, the nucleus became more vesicular, the nuclear reticulum became finer and more widely meshed, and the nucleolus lost its chromatin and appeared as a plastin body; meanwhile the cytoplasm changed from light blue or lilac to deeper lilac color. Without prejudice as to the nature of the small cell of the splenic nodule, whether a small lymphocyte or a small hemocytoblast, the evidence seems conclusive that this small cell was the ancestor of the larger typical hemocytoblast which changed into a normoblast within the splenic sinuses.

The hemocytoblast in the spleen underwent the well known changes characteristic of erythropoiesis (figs. 17 and 18). These changes were identical in the splenic sinuses, marrow sinuses (fig. 20) and hepatic sinuses (fig. 22). Both cytoplasm and nucleus became condensed. The chromatin blocks became arranged peripherally, giving the nucleus the cart-wheel character typical of the erythroblast. Meanwhile, in eosin-azure preparations, the lilac color of the cytoplasm changed to pink or red. The process of nuclear and cytoplasmic condensation continued until the typical normoblastic stage with a dense chromatic nucleus was attained. At this stage, more frequently in the case of the normoblast of the hepatic sinuses, loss of nucleus in the formation of the erythroplastid was preceded by karyorrhexis; in this condition the nucleus frequently assumed a trefoil or multiglobular shape.

COMMENT

This case illustrates the reversal of the phylogenetic history of the blood-forming tissues. In phylogeny the fundamental blood-forming organ, the spleen, apportions its functions of lymphocytopoiesis and erythrocytopoiesis at the higher levels, respectively, among lymph nodes and bone marrow. It retains prominently in the mammalian adult only the functions of lymphocyte and monocyte formation. Since the lymph nodes also perform these functions to a high degree, the spleen represents as regards its primary function of blood formation only a vestigial organ. However, by virtue of its reticular stroma, its lymphocyte parenchyma and its sinusoidal venous circulation, it retains its evolutionary and fetal potentiality for the formation of the red cells. In

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EXPLANATION OF PLATE 4 (CASE 2, ADENOCARCINOMA OF PROSTATE)

Fig. 16.—Group of six lymphocytes from a splenic nodule. The two larger lymphocytes (above at the right) are approaching the size and features of the hemocytoblast. Helly fixation; hematoxylin and eosin stain; × 1,350.

Fig. 17.—Group of six cells from a splenic sinus. The two larger cells are typical hemocytoblasts. The smaller cells with pyknotic nuclei are normoblasts. The two cells of intermediate size above at the right are erythroblasts. Helly fixation; hematoxylin and eosin stain; × 1,350.

Fig. 18.—Similar group of cells from a splenic sinus.

Fig. 19.—Group of five cells from a splenic sinus, including four typical hemocytoblasts and one erythroblast (below at right). Helly fixation; eosin-azure stain; × 1,350.

Fig. 20.—Group of six cells from a marrow sinus, including two typical hemocytoblasts (at left), three erythroblasts and one normoblast (below at right). Helly fixation; hematoxylin and eosin stain; × 1,350.

Fig. 21.—Large hemocytoblast, ancestor of the megakaryocyte; × 1,350.

Fig. 22.—Group of six cells from a hepatic sinus, including three hemocytoblasts, one erythroblast (above) and one normoblast. Helly fixation; hematoxylin and eosin stain; × 1,350.

this case of adenocarcinoma of the prostate both the lymph nodes and the bone marrow were largely eliminated from the hemocytopoietic system by reason of extensive metastases, and the spleen was stimulated to assume as a compensatory measure its original erythrocytopoietic activity. The condition roughly parallels the evolutionary level of the Amphibia in which the bone marrow has only slight erythropoietic activity, the spleen being the dominant organ in the production of red cells. From another point of view this case represents a natural experiment in which most of the lymph nodes and large portions of the bone marrow have been eliminated from the hemopoietic system. The resulting condition provides the stimulus for the compensatory hyperfunction of the remaining potentially erythrocytopoietic tissue, namely, the spleen.

The interpretation of the small lymphocyte of the splenic follicles as the ancestor of the erythrocytogenic hemocytoblast is based on two sets of data: (1) transitional stages; (2) the phylogeny of hemocytopoietic tissues. The evidence from transitional stages must be evaluated in connection with the spatial relationships and in comparison with conditions in the lymph nodules of normal active lymph nodes and the normal spleen.

As described in a foregoing paragraph, the nodules of the erythrocytopoietic spleen in case 2 lacked germinal centers. The nodules consisted almost exclusively of typical small lymphocytes. Along the periphery occurred a number of typical hemocytoblasts; in the region between the central and the peripheral area occurred numerous cells that were transitional between the small lymphocyte and the hemocytoblast with respect to both size and structure. In the extranodular regions, especially numerous in the venous sinuses, occurred large numbers of hemocytoblasts mingled with cells in all stages of maturation into erythrocytes. This evidence, considered in relation to the fact that many of the nodules had disappeared and that those which persisted were relatively small, suggests the conclusion that the nodules were being used up in the production of hemocytoblasts by metamorphosis of the small lymphocytes.

Considering now the nodules of normal lymph nodes and the normal spleen, the following facts emerge. These nodules contain large germinal centers, composed chiefly of large cells with lightly staining nuclei cytologically identical with hemocytoblasts. These cells, here designated as lymphoblasts, represent free derivatives of the reticular stroma of this region. While the cells are generally of large size, taken as a group they include small, medium-sized and large varieties. They are collectively characterized by a vesicular nucleus, with delicate reticulum and one or several nucleoli. The small varieties may grow to larger size. Only the cells of maximum size divide; the stages in mitosis are numerous. Peripheral to the germinal center occurs a compact layer of

variable width consisting of concentric rows of small lymphocytes. These represent daughter cells of the hemocytoblasts. As typical small lymphocytes they find their way into the medullary cords and sinuses and eventually into the blood stream. Meanwhile a certain number enlarge to become large lymphocytes cytologically identical with the original lymphoblasts (hemocytoblasts). In view of this history it becomes meaningless to describe a small lymphocyte in terms of age; it is both the offspring of a hemocytoblast and the parent of one. The small lymphocyte of the lymph node, splenic parenchyma and peripheral blood is a relatively undifferentiated cell capable of the expression of any one of its multiple developmental potentialities depending on environmental stimuli. Thus it may be ancestral to an erythrocyte, a granulocyte or a monocyte. Accordingly, it is misleading to speak of the small lymphocyte of the blood as a definitive cell comparable to the erythrocyte. Both nuclear and cytoplasmic features mark it as a relatively undifferentiated cell. It represents in fact a hemocytoblast reduced in size presumably for purposes of more ready transportation. The smaller forms may enlarge, thus contributing the numerous medium-sized ones.

The foregoing conclusion is not invalidated by the fact of the occurrence of degenerating and senile small lymphocytes in the lymph nodes, in the spleen and in the peripheral blood. Degenerate forms are especially numerous in areas of very active production. Hu and Ch'in [9] reported that 21.2 per cent of the small lymphocytes in the inguinal lymph nodes of the rat were degenerate, and 28.9 per cent of those in the spleen. The abortive result represents a casualty of rapid formation. Young cells as well as old cells may be defective or injured and as a result degenerate. Similarly, in the blood stream a certain small number may degenerate; these are the senile or "definitive" type recognized by Hu and Ch'in [8] and Wiseman.[10] Hu and Ch'in gave the percentage in rat's blood as 0.15. The striking and significant fact in the work of Hu and Ch'in with supravitally stained preparations relates to the small number of so-called definitive forms, and the large number of intermediate forms.

According to Wiseman,[10] 45 per cent of the small lymphocytes of the peripheral blood of the rabbit are of "mature" type, judged by the relatively lesser degree of cytoplasmic basophilia and the decreased content of the mitochondria in supravital preparations of such cells as compared with the younger forms. About 5 per cent are recognized as in the "end phase," lacking all of the characteristics of youth and maturity. There can be no question regarding the degeneration of a certain small

9. Hu, C. H., and Ch'in, K. Y.: Proc. Soc. Exper. Biol. & Med. **30**:433, 1933.

10. Wiseman, B. K.: J. Exper. Med. **54**:271, 1931; Folia haemat. **46**:346, 1932.

percentage of circulating lymphocytes. However, the so-called mature small lymphocytes may still have the youthful character of possessing metachromatic granules as revealed in Wright's stain. And cytoplasmic basophilia is not necessarily indicative of youth; the cytoplasm of the reticular cell ancestor of the lymphocyte is less basophilic than that of the free young lymphocyte, while the cytoplasm of the plasma cell is more basophilic than that of the ancestral lymphocyte. The best single criterion of the age of the lymphocyte is the character of the nucleus. The degenerating lymphocyte contains a relatively small, deeply pyknotic nucleus.

Approached from the standpoint of the evolutionary history of the blood-forming tissues the matter appears thus: The spleen is the fundamental erythrocytogenic organ from lower fishes through amphibians. In reptiles and birds and even in certain mammals, e. g., the bat, the hedgehog, the opossum, it maintains a considerable degree of activity as a site of red cell production. Also in fetal life in man it functions largely as an erythrocytopoietic tissue. Only when marrow appears in phylogeny at the level of the amphibians, as an incident of hollow bones, in human ontogeny during the second month, is the production of red cells partly shifted to this tissue. At the level of the mammals the originally multiple function of the spleen becomes apportioned to the lymph nodes and the bone marrow; as regards the original specific function of forming blood the spleen of the mammal represents a vestigial organ.

The erythrocytopoietic lymph nodes in case 1 contrast sharply with those in case 2. Whether the difference signifies only separate phases of the same process or something more fundamental remains uncertain. Both were active in the formation of red cells, and the normal demarcation between the cortex and the medulla was largely obliterated; but otherwise the nodes were very dissimilar. In case 1 (leukemia) the parenchyma was uniformly moderately dense; the sinuses were not especially prominent and contained relatively few erythrocytes. Megakaryocytes were very rare, and macrophages were not numerous. Maturing erythrocytes were uniformly scattered among the lymphocytes of the parenchyma. This lack of segregation of maturing erythrocytes in small groups was perhaps the most characteristic feature of these lymph nodes. Typical hemocytoblasts, such as occurred in large numbers in case 2, were relatively rare. Those that occurred, however, appeared in small groups. These lymph nodes did not closely resemble typical hemolymph nodes. The large number of cells that were transitional between typical small lymphocytes and erythroblasts suggests that in these nodes the erythrocytes differentiated directly from small and medium-sized polyvalent lymphocytes instead of from hemocytoblasts as in case 2.

The tumor-free "lymph nodes" in case 2 (adenocarcinoma of the prostate) were typical hemolymph nodes. The sinuses were well filled with blood; megakaryocytes were numerous; cells transitional between small lymphocytes and hemocytoblasts and between the latter and erythroblasts were abundant. Both hemocytoblasts and maturing erythrocytes were seen occurring in groups. On the basis of the information from an earlier comparative study of hemolymph nodes in the sheep, rabbit and dog and man (Jordan [11]) the conclusion is suggested that the nodes in case 2 signify later stages of the process of erythrocytopoietic metaplasia represented in case 1.

The evidence from these two cases of extramedullary formation of blood in man emphasizes the relative independence of the two chief aspects of marrow hemopoiesis: erythrocytopoiesis and granulocytopoiesis. Here the two processes are separated as at the lower evolutionary levels and in the mammalian fetus during the period when the spleen is active in the production of red cells. The very intimate association of the two processes in the bone marrow of adults obscures their essential independence. However, both erythrocytes and granulocytes arise from apparently identical ancestors, the lymphoid hemoblasts. But the differentiation of granulocytes occurs extravascularly; the production of erythrocytes, generally only intravascularly. The differential factors leading respectively to red cell or to granulocyte formation are apparently entirely environmental.

In the primitive spleen of the cyclostome fishes erythrocytopoiesis and granulocytopoiesis are associated; their spleen represents a myeloid tissue equivalent to the bone marrow of mammals. In the lung fishes the spleen still includes both tissues, but granulocytopoiesis is also very active in the wall of the intestine (Jordan and Speidel [12]). In elasmobranch fishes granulocytopoiesis is restricted to the stroma of the gonads and formation of red cells occurs only in the spleen. In most teleost fishes red cells are formed in the spleen and granulocytes in the mesonephron; in some teleosts both processes occur to a variable degree in the kidney. In most salamanders the formation of red cells is restricted to the spleen and the formation of granulocytes to the subcapsular stroma of the liver; in a few salamanders, e. g., Proteus, the differentiation of granulocytes is restricted to the kidney. In frogs, during the greater part of the year, the red cells arise in the spleen and the granulocytes to a large extent in the marrow; however, for a brief period after hibernation both processes occur in the bone marrow. At all of these levels the maturation of the red cells occurs to a variable extent in the periph-

11. Jordan, H. E.: J. Morphol. & Physiol. **44**:89, 1927.

12. Jordan, H. E., and Speidel, C. C.: Am. J. Anat. **46**:355, 1930; J. Morphol. & Physiol. **51**:319, 1931.

eral blood stream (Jordan [13]). Furthermore, at all levels there may be considerable granulocytopoietic activity in the wall of the intestine. In view of these facts it is in accord with a more precise terminology to speak of erythrocytopoietic metaplasia and granulocytopoietic metaplasia rather than myeloid metaplasia. The metaplasia of the lymph node and spleen in cases 1 and 2 was of the erythrocytopoietic type.

Perhaps the most significant feature of case 1 was the condition of the bone marrow; the bulk was lymphoid. The marrow had the appearance largely of lymphoid tissue; the lymph nodes and portions of the spleen had the appearance of red bone marrow; the lymph nodes had undergone an erythrocytopoietic metaplasia, the marrow a lymphoid metaplasia. The dominating cell of the bone marrow was a typical small lymphocyte. The lymphocytes appeared to be more closely aggregated about arterioles, suggesting lymph nodules. Hemocytoblasts and erythroblasts, while numerous in certain regions, occurred in relatively small numbers. In view of the large percentage of small lymphocytes in the blood the conclusion might be drawn that the lymphocytes of the marrow represented cells filtered out of the blood stream. If such a conclusion were justified it would support the idea that the normal fate of the lymphocyte is largely to serve as an ancestor of the red cell in the venous sinuses of the bone marrow. This is in part the fate of the lymphocyte of anuran amphibians (Jordan [14]). To account for the accumulation and persistence of lymphocytes in this marrow it is necessary to assume that the pathologic condition rendered impossible the differentiation at normal tempo of the hemogenic lymphocytes into erythrocytes. However, the possibility that these marrow lymphocytes represented cells of local origin cannot be ignored, especially in view of the fact that the lymphocytes of the lymph nodes and spleen were largely converted into red cells locally. However interpreted, the evidence suggests a very intimate relationship between erythrocytopoietic and lymphoid tissues. Here apparently, as in lower forms in which erythrocytopoiesis is restricted to the spleen, the lymphoid and erythroid tissues were potentially one and the same tissue.

SUMMARY

Two cases of extramedullary hemocytopoiesis with a very different fundamental pathology are described. In case 1 (acute leukemia) erythrocytopoietic metaplasia was pronounced in the lymph nodes. In case 2 (adenocarcinoma of the prostate) in which many of the lymph nodes and large portions of the marrow had been obliterated by metastases, the spleen was the seat of erythrocytopoietic metaplasia. These

13. Jordan, H. E.: Quart. Rev. Biol. **8**:58, 1933.
14. Jordan, H. E.: Am. J. Anat. **25**:437, 1919.

two cases in a sense complement each other. They represent natural experiments in which in one case the bone marrow and the spleen have been largely removed from the hemopoietic system, leaving the lymph nodes for compensatory erythrocytopoietic function; in the other case the marrow and the lymph nodes have been replaced, leaving the spleen unimpaired. In both cases the small lymphocyte functions as the ancestral cell of the erythrocyte.

In case 1 (leukemia) the lymph nodes especially, to some degree the spleen, had undergone erythroid metaplasia; the bone marrow showed extensive lymphoid metaplasia. The evidence emphasizes the intimate relationship between myeloid and lymphoid tissue with respect to erythrocytogenesis. The ancestor of the red cell was in both tissues a small lymphocyte, the lymphoid hemoblast. Such a condition parallels that of earlier ontogenetic and lower phylogenetic stages in which the lymphoid spleen is the locus of red cell formation.

In case 2 (adenocarcinoma of the prostate) the lymph nodes had been largely replaced by tumor tissue and the bone marrow was greatly restricted; the spleen had undergone a high degree of erythroid metaplasia, the formation of red cells being very active. Here the small lymphocyte first became a typical hemocytoblast, which then matured into an erythrocyte. The few small persistent lymph nodes had become converted into typical hemolymph nodes, with much blood in the sinuses, large numbers of megakaryocytes and very active transformation of small lymphocytes into erythrocytes. The evidence emphasizes the independence of erythrocytopoiesis with respect to granulocytopoiesis. The "myeloid" metaplasia of the spleen and lymph nodes concerned only the production of red cells.

The evidence supports the claim of the erythrocytogenic capacity of the small lymphocyte and the interpretation of this cell as a relatively undifferentiated one with multiple developmental potentialities.

CHRONIC CICATRIZING ENTERITIS

WITH INVOLVEMENT OF THE CECUM AND THE COLON

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The intestinal lesions varyingly described as regional ileitis, chronic cicatrizing enteritis and nonspecific granuloma of the intestine have received an increasing amount of attention since they were first described by Braun,[1] in 1909, on the basis of one case in which inflammation of the sigmoid flexure was treated by surgical removal and two cases in which the mass felt at operation in the cecum disappeared without resection. The description of this condition by Braun threw light on certain conditions simulating malignant changes in the intestine, which cleared up with palliative treatment, such as short circuiting and colostomy, examples of which had been reported by Moynihan [2] and Mayo Robson [3] some years previously.

Until after the war but little attention was devoted to this condition. With increased interest in malignant disease, the frequency with which this lesion simulated carcinoma brought more and more attention to it. A review of the subject was made by Tietze,[4] in 1920, who added a number of cases of his own, in two of which the condition was localized in the cecal region, and in all of which the lesions simulated malignant disease and were found to be examples of "non-specific granuloma." [5]

A second review of the infectious granulomas, not only those of the intestinal tract but also those throughout the abdominal cavity, was presented in 1931 by Mock,[6] who brought the subject well up to date.

The picture presented by this lesion, which is better known as chronic cicatrizing enteritis,[7] although varied, nevertheless has a number of fairly constant characteristics. The etiology is uncertain. A number of factors have been incriminated, from inflammatory processes in the

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From the Laboratory of Pathology of the New England Deaconess Hospital.

1. Braun, Heinrich: Deutsche Ztschr. f. Chir. **100**:1, 1909.
2. Moynihan, B.: Edinburgh M. J. **21**:228, 1907.
3. Robson, A. W. M.: Brit. M. J. **1**:425, 1908.
4. Tietze, Alexander: Ergebn. d. Chir. u. Orthop. **12**:211, 1920.
5. Moschcowitz, Eli, and Wilensky, A. O.: Am. J. M. Sc. **166**:48, 1923.
6. Mock, H. E.: Surg., Gynec. & Obst. **52**:672, 1931.
7. Harris, F. I.; Bell, G. H., and Brunn, Harold: Surg., Gynec. & Obst. **57**:637, 1933.

neighborhood of the appendix to the use of certain types of suture. In many of the reported cases the condition followed an abdominal operation.

In the more characteristic forms there is fairly close restriction to the region of the ileocecal valve, although a number of cases in which the lesion was found elsewhere in the intestinal tract, and especially in the sigmoid flexure, have been reported. Even in cases with extensive cecal involvement, the appendix may show no abnormalities.

Since the most common point of involvement is the lower part of the ileum, the name regional ileitis [8] has come into prominence.

The symptomatology is usually vague, with abdominal cramps and other evidences of obstruction as prominent features, although these are not constant. The presence of a mass is also fairly frequent. Thus, the most common diagnosis is carcinoma, although tuberculosis and syphilis have also been confused with this condition. Usually the patient has not lost an appreciable amount of weight, is not prostrated and makes an uneventful recovery after the obstruction is removed. In some cases the development of fecal fistulas, either postappendical or spontaneous, has been a prominent feature of the clinical course of the disease.

From the standpoint of pathology, there are a number of points in common, in spite of the variation of the detailed picture. Usually the involved portion of the intestine is firmly fixed to the adjacent structures. Often, through chronic inflammatory changes in the tissues and the development of adhesions in the neighborhood of the lesion, an appreciable mass is built up. The lymph nodes draining the region show evidence of hyperplasia.

On opening the intestine, varying degrees of thickening of the wall and of ulceration of the mucosa, with stenosis, are noted.

Roentgen examination not infrequently reveals changes simulating those in an obstructing malignant lesion. There is no definite age limit, there being a wide distribution in regard to age. There is also no predilection for either sex.

We present one case which is of interest because of the involvement of the entire cecum and all the ascending colon, without any appreciable change on the proximal side of the ileocecal valve other than a moderate degree of hypertrophy of the muscularis produced through partial obstruction at the valve.

REPORT OF A CASE

History.—A woman, 62 years of age, was admitted to the New England Deaconess Hospital on Nov. 28, 1933, under the care of Dr. Howard M. Clute, surgeon of the Lahey Clinic. Eighteen years before, she had undergone cholecys-

8. Crohn, B. B.; Ginzburg, Leon, and Oppenheimer, G. D.: J. A. M. A. **99**:1323, 1932.

tostomy for the relief of pain in the right upper quadrant with jaundice. She had had occasional attacks of abdominal distress since that time, which were different from the previous pain and without jaundice. She remained fairly well until four years before examination, when she had attacks of abdominal cramps, constipation and much flatus for several months. After these attacks passed without treatment, she remained well until two and one-half months before examination, when another attack of mild abdominal cramps occurred, each lasting for from several seconds to a minute. This was accompanied by marked constipation. Diarrhea was induced by catharsis. There was no vomiting. Within this period she lost about 5 pounds (about 2.3 Kg.).

The results of the physical examination were essentially negative, with the exception of a scar in the right upper quadrant. The abdominal wall was lax and flabby. Some tenderness was found in the right lower quadrant. The apparently gas-filled bowel was readily palpable in the right lower quadrant. Pelvic and rectal examinations gave essentially negative results.

Roentgen examination on December 30 showed a barium sulphate enema filling the colon as far as the hepatic flexure. The colon was dilated and atonic, with apparently a definite lesion at the hepatic flexure. Only a thin trickle of barium passed this point. The cecum and the ascending colon were distended with air. A roentgen diagnosis of carcinoma of the hepatic flexure was made, which reenforced the clinical impression of carcinoma of the cecum. The results of laboratory examinations were essentially negative.

Operation, performed by Dr. Clute on Jan. 4, 1934, was somewhat difficult because of numerous adhesions resulting presumably from the previous cholecystostomy. A mass about the size of a lemon was found involving the cecum just above the ileocecal junction. There was no evidence of metastasis to any organ, and as the lesion was freely movable resection was done. This included about 6 inches (15 cm.) of the terminal part of the ileum, the cecum, the ascending colon and a portion of the transverse colon. The resection was of the Mikulicz type, about 4 inches (10 cm.) of ileum being sutured to the transverse colon, with the usual double-barreled colostomy. The postoperative diagnosis was carcinoma of the cecum. A moderate degree of postoperative shock was readily controlled by venoclysis and blood transfusion. The subsequent course was good.

Pathologic Report.—A portion of bowel 36 cm. long, with a portion of the omentum attached to the distal end and a considerable mass of adherent fat and mesentery, was examined. One mass of firm fat surrounded the proximal end. On opening the lumen of the intestine, the specimen was seen to consist of 6 cm. of terminal ileum, the cecum, the ascending colon, and a portion of the transverse colon. The ileum was dilated up to 10 cm. in circumference; its wall was thickened and hypertrophied, but there was no evidence of inflammatory change. There was a prominent ring of fibrous tissue and muscle encircling the ileocecal valve. The lumen here measured barely 0.5 cm. in diameter (fig. 1). The caput of the cecum was practically obliterated by contraction, and an irregular tunnel with ulcerated walls led into a mass of firm, injected fat at the normal site of the appendix. Section through the mass of inflammatory fat revealed this passage to be about 2 cm. long; it was fairly straight, with shaggy necrotic sides. This apparent appendical lumen ended in the midst of firm, fibrous tissue which extended throughout the mass of fat surrounding the ileocecal region.

The entire cecum and ascending colon were markedly constricted, the circumference being about 1.5 cm. Not only was there constriction, but there was also considerable shortening, as was evidenced by the plicated condition of the muscu-

laris (fig. 2). This combination of circumferential and longitudinal constriction indicated a fairly long-standing fibrotic process. The mucosa was brownish red and thin, and in places it was apparently absent, leaving bare fibrous tissue.

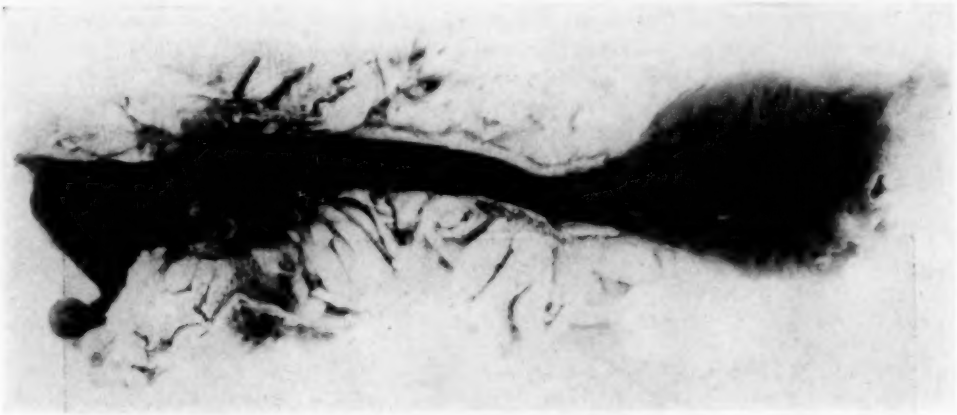

Fig. 1.—Lower part of the ileum, the ileocecal valve, the cecum, the ascending colon and a portion of the transverse colon. The probe lies in the lumen of the appendix.

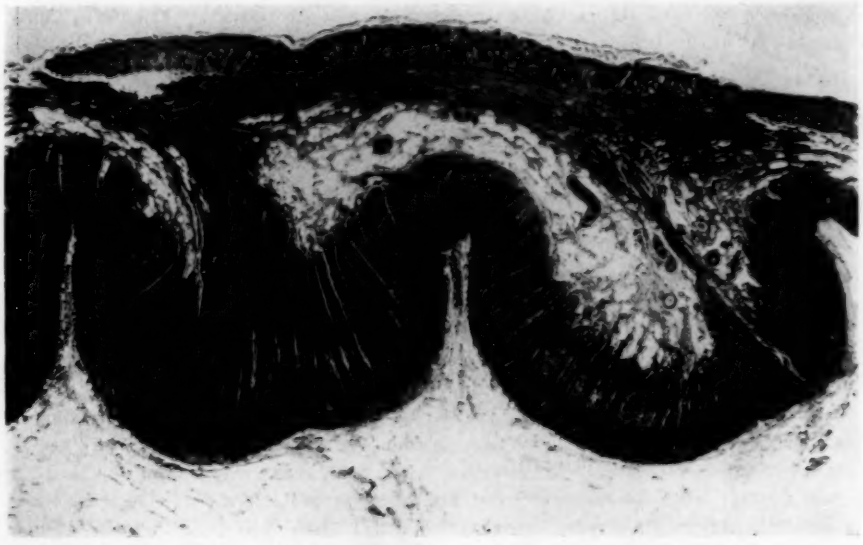

Fig. 2.—Cicatrized ascending colon just below the junction with the normal colon; reduced from a magnification of × 25.

At the hepatic flexure there was an extraordinarily sharp and rapid change from the atrophic mucosal surface to approximately normal intestinal surface. Within a distance of about 2 cm. the colon practically regained its normal circum-

ference and the transition from the atrophic to the normal mucosa was as abrupt as though it had been cut with a knife.

Microscopic Observations.—Sections of the ileum were essentially normal, except for moderate hyperplasia of the musculature. The colon beyond the hepatic flexure was normal. The cecum and the ascending colon were essentially alike. The mucosa was markedly atrophic, and in numerous foci the epithelium was completely lacking. Dilated glands were scattered elsewhere, the lumens of which contained numerous polymorphonuclear leukocytes. A few of these glands in the region of the appendical orifice showed metaplasia of the epithelium, with transition to a high columnar cell with a large nucleus and little evidence of mucous secretion, suggesting the glands seen in certain carcinomas of the large intestine (fig. 3).

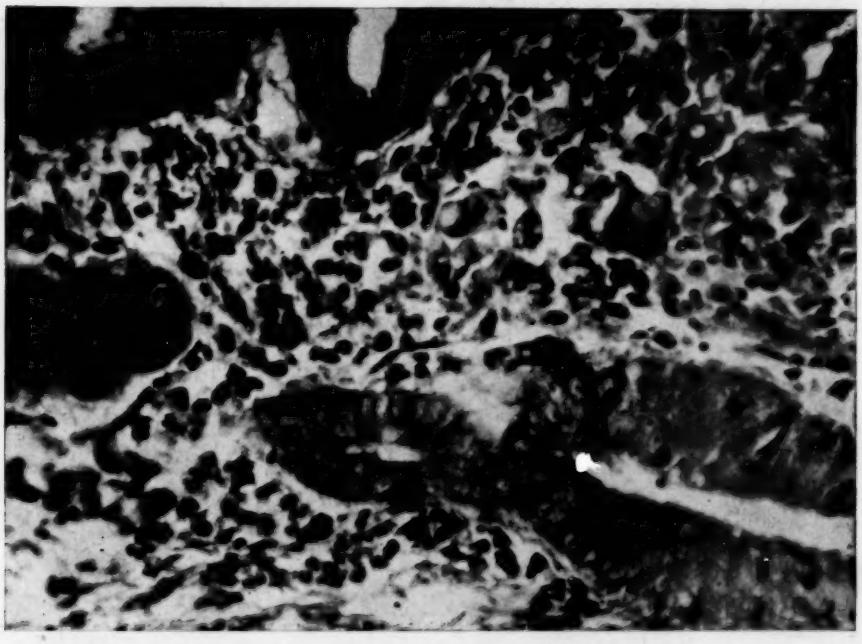

Fig. 3.—Metaplasia of the epithelium at the ileocecal valve; reduced from a magnification of × 600.

However, no distinct evidence of invasion was found; there was no appreciable proliferation, and mitotic figures were absent. Much of the mucosa had been replaced by rather avascular granulation tissue with numerous plump fibroblasts and relatively little intercellular substance, accompanied by heavy infiltration by polymorphonuclear leukocytes, lymphocytes and plasma cells. Eosinophils were frequently encountered, particularly in the submucosa, and scattered mast cells were present. There were a few irregularly scattered foci of definite necrosis, some with a moderate amount of fibrins. Rare giant cells of the foreign body type were present in the submucosa, some of which contained vacuoles. At the point of junction of the normal colon and the involved ascending colon there was a sharp demarcation of the mucosa. A few small ulcers extended down to, or slightly below, the tunica propria, with fairly extensive extravasation of red cells beneath. The leukocytic reaction was slightly more intense here than elsewhere.

Synopsis of Reported Cases of Chronic Cicatrizing Enteritis Involving the Cecum and the Colon

Case	Author	Site of Lesion	Previous Operation	Appendix	Signs and Symptoms
1	Harris, Bell and Brunn [7]	Portion of ascending colon, cecum, ileocecal valve and portion of ileum	Appendectomy	Absent	Acute intra-abdominal symptoms 6 months later
2	Körte, W.: Arch. f. klin. Chir. **118**: 138, 1921	Portion of ascending colon, cecum, ileocecal valve and portion of ileum	None	Normal	Abdominal pain
3	Wilensky, A. O., and Moscheowitz, Eli: Am. J. M. Sc. **173**: 374, 1927	Portion of ascending colon, cecum, ileocecal valve and portion of ileum	Appendectomy	Absent	Fistula and obstruction 3 months later
4	Erdmann, J. F., and Burt, C. V.: Surg., Gynec. & Obst. **57**: 71, 1933	Portion of ascending colon, cecum, ileocecal valve and portion of ileum	Appendectomy	Absent	Cramps in abdomen 6 years later
5	Gordon, Donald: Ann. Surg. **97**: 130, 1933	Portion of ascending colon, cecum, ileocecal valve and portion of ileum	Appendectomy	Absent	Intestinal obstruction 3 years later
6	Coffen, T. H.: J. A. M. A. **85**: 1303, 1925...	Portion of ascending colon, cecum and portion of ileum	Appendectomy	Absent	Intestinal obstruction
7	Jefferies, J. F.: J. M. A. South Africa **2**: 184, 1928	Portion of ascending colon, cecum and portion of ileum	None	Involved	Intestinal obstruction
8	Koch [9]	Entire ascending colon, cecum and ileocecal valve	None	Not mentioned	Symptoms of gallbladder disease; colicky pain and constipation
9	Moscheowitz and Wilensky [5]	Entire ascending colon, cecum and ileocecal valve	Appendectomy	Absent	Abdominal pain and intestinal obstruction 9 months later
10	Nemilov, Alexander: Arch. f. klin. Chir. **153**: 346, 1928	Portion of ascending colon, cecum and ileocecal valve	None	Obliterated	Abdominal pain and intestinal obstruction
11	Körte, W.: Arch. f. klin. Chir. **118**: 138, 1921	Portion of ascending colon and cecum....	None	Involved	Abdominal pain
12	Moscheowitz and Wilensky,[5] Erdmann's case	Portion of ascending colon and cecum....	Appendectomy	Absent	Abdominal pain and intestinal obstruction 3 months later
13	Läwen, A.: Deutsche Ztschr. f. Chir. **129**: 221, 1914	Portion of ascending colon and cecum....	None	Involved	Abdominal pain
14	Läwen, A.: Deutsche Ztschr. f. Chir. **129**: 221, 1914 (Law's case)	Portion of ascending colon and cecum....	None	Not mentioned	?
15	Läwen, A.: Deutsche Ztschr. f. Chir. **129**: 221, 1914 (Schmidt's case)	Portion of ascending colon and cecum....	None	Normal	?
16	Golob, Meyer: M. J. & Rec. **135**: 390, 1932	Cecum and ileocecal valve.....	None	Normal	Abdominal pain
17	Braun [1]	Cecum	None	Not mentioned	Abdominal pain
18	Braun [1]	Cecum	None	Not mentioned	Abdominal pain
19	Tietze [4 *]	Cecum with purse-string suture.....	Appendectomy	Absent	Abdominal pain
20	Tietze,[4] Goto's case.....	Cecum	None	Not found	Abdominal pain
21	Mock [6]	Cecum with purse-string suture.....	Appendectomy	Absent	Intestinal obstruction 3 years later
22	Körte, W.: Arch. f. klin. Chir. **118**: 138, 1921	Cecum	None	Not mentioned	Abdominal pain
23	Nemilov, Alexander: Arch. f. klin. Chir. **153**: 346, 1928	Cecum	Herniotomy	Normal	Abdominal pain 2 years later
24	Moscheowitz and Wilensky [5]	Ascending colon	None	Obliterated	Cramps and vomiting

* Tietze also reported four cases of typhlitis.

The muscularis was thrown into folds by longitudinal contraction of the intestine and showed extensive fibroblastic proliferation, with some edema. There were numerous fairly thick-walled blood vessels and dilated lymphatics. Polymorphonuclear leukocytes were scattered diffusely through the tissue, together with monocytes, occasional plasma cells, eosinophils and lymphocytes. Toward the serosa, mast cells were a fairly prominent feature. Large collections of lymphocytes were observed in frequent foci, with the formation of germinal centers. Giant cells of the foreign body type were seen both within, and adjacent to, these foci.

The serosa and the subserosa were markedly edematous and were thickened by a rather diffuse, loose, fibrous tissue with some evidence of fibroblastic proliferation. There were numerous large, dilated lymphatics, many of which contained polymorphonuclear leukocytes in their lumens, and in a few the Gram-Weigert stain showed gram-positive cocci in pairs and short chains. The same type of cellular infiltration occurred here as in the mucosa, with similar focal accumulation of lymphocytes. The adjacent fat was heavily fibrosed and showed infiltration by the various types of inflammatory cells already described. Minute foci of necrosis and polymorphonuclear infiltration were observed in the subserosa and the serosa.

The microscopic diagnosis was: chronic cicatrizing enteritis, with a focus of metaplasia of the epithelium; chronic appendicitis and periappendicitis, with necrosis.

COMMENT

We regard this case as distinct from any yet reported, because of the sharp localization of the condition to the cecum and the ascending colon and because of the remnants of a destructive, suppurative process in the vestiges of the appendix.

The sequence of events we believe to be somewhat as follows: The process began four years before the patient was examined when the attack of abdominal pain and cramps probably indicated acute appendicitis. This failed to heal properly and became the focus from which gradual extension of the inflammatory process occurred through the lymphatics and tissue spaces, with increasingly greater involvement of the large intestine. Symptoms were not marked until the low grade inflammatory process had produced a sufficient degree of constriction of the ileocecal valve and the large intestine to induce partial intestinal obstruction. This obstruction, once developed, rapidly increased in severity and led to the patient's admission to the hospital. Roentgen examination revealed the extent of the lesion, the barium enema reaching only to the hepatic flexure. What was regarded by the roentgenologist as an air-filled cecum and ascending colon was the greatly dilated, gas-filled terminal part of the ileum. The hard, inflammatory mass of fat built up about the inflamed appendix and cecum simulated malignant disease on palpation through the abdominal wall.

We did not attempt bacteriologic studies of the tissue removed, because of the obvious chronicity of the process, which would have permitted any originally causative organism to die out long before, and because the absence of mucosa over a large stretch of intestine would

permit access to the tissues of all types of organisms from the intestinal contents. It is not remarkable that focal necrosis and evidence of acute inflammation were found scattered throughout the intestinal wall, as there must have been a continual access of organisms to the unguarded tissues. While we succeeded in demonstrating streptococci with the Gram-Weigert stain within some lymphatics showing heavy polymorphonuclear infiltration, we do not assign an etiologic rôle to these, as there is no way of ruling them out as secondary invaders.

One point of interest is the metaplasia of the epithelium, which took place, in all probability, as a result of the long-standing abnormal condition under which the mucosa of the cecum had attempted to regenerate and maintain function. It is possible that, had this process continued longer, there might have been transformation to a malignant process. There is a strong similarity in the change seen here and that seen in the early stages of malignant degeneration of the common rectal polypus.

A study of the cases previously reported shows involvement of the cecum and the colon to be relatively infrequent. However, well established cases of this type have been reported by a number of authors; these are summarized in the table.

The cases most closely resembling ours are those of Koch [9] and of Moschcowitz and Wilensky.[5]

An important point brought out by a study of this group of cases is the high frequency of appendical involvement, emphasizing somewhat the importance of the appendical lesion in our case. Of the group, nine patients had undergone appendectomy; five showed pathologic changes in the appendix; in the case of five the appendix was not mentioned, and only four had appendixes noted as normal. In the nine cases in which the enteritis followed appendectomy, the onset of the symptoms appeared, on the average, thirteen months after the operation.

SUMMARY AND CONCLUSIONS

A case of chronic cicatrizing enteritis is reported, in which the condition apparently developed after appendicitis and involved the cecum, the ileocecal valve and the ascending colon.

The exact etiology is unknown. The recovery of organisms from the lesion would have been without significance, because of the ease with which the ulcerated mucosa could be traversed.

The chief importance of this lesion lies in its mimicry of carcinoma. In all probability, apparent cases of certain intestinal cancers may be explained by the fact that a lesion of this nature was mistaken for carcinoma.

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9. Koch, Joseph: Arch. f. klin. Chir. **70**:876, 1903.

HEPATIC CHANGES ASSOCIATED WITH DECOMPRESSION OF OBSTRUCTED BILIARY PASSAGES

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The recent literature contains numerous references to a group of terminal clinical syndromes vaguely designated as "liver deaths," which may occur following various operative procedures on the biliary passages. Excellent descriptions of these phenomena have been presented by Cave,[1] Behrend,[2] Stanton,[3] Heyd,[4] Connell,[5] Walters,[6] Walters and Parham,[7] Helwig and Schutz,[8] Schutz, Helwig and Kuhn,[9] Doran, Lewis, Denneen and Hanssen,[10] Bryan,[11] Eiss[12] and Weir and Walters.[13] The symptoms manifested by patients with these conditions have been grouped by Heyd under three headings. One group occurs in patients operated on for the relief of biliary stasis, shortly following which they slowly pass into stupor and coma, death being similar to cholemic death in unrelieved obstructive jaundice. Schutz, Helwig and Kuhn supported in general Heyd's classification but pointed out that no serious attempt has been made to investigate the morphologic changes present in the liver of these patients and that few substantial facts relative to the actual mechanisms at work in the production of

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From the pathological laboratories of the Jefferson Medical College and Hospital, the Jefferson Hospital Tumor Clinic and the Philadelphia General Hospital.

1. Cave, H. W.: Ann. Surg. **84**:371, 1926.
2. Behrend, M.: Surgical Diseases of the Gallbladder, Liver and Pancreas, Philadelphia, F. A. Davis Company, 1927.
3. Stanton, E. M.: Am. J. Surg. **8**:1026, 1930.
4. Heyd, C. G.: Am. J. Obst. & Genec. **19**:203, 1930; J. A. M. A. **97**:1847, 1931; Surg., Gynec. & Obst. **57**:407, 1933.
5. Connell, F. G.: Ann. Surg. **94**:363, 1931.
6. Walters, W.: Ann. Surg. **94**:55, 1931.
7. Walters, W., and Parham, D.: Surg., Gynec. & Obst. **35**:605, 1922.
8. Helwig, F. C., and Schutz, C. B.: Surg., Gynec. & Obst. **55**:570, 1932.
9. Schutz, C. B.; Helwig, F. C., and Kuhn, H. P.: J. A. M. A. **99**:633, 1932.
10. Doran, W. T.; Lewis, K. M.; Denneen, E. V., and Hanssen, E. C.: Ann. Surg. **98**:321, 1933.
11. Bryan, W. A.: Ann. Surg. **98**:342, 1933.
12. Eiss, S.: Ann. Surg. **98**:348, 1933.
13. Weir, J. F., and Walters, W.: J. A. M. A. **102**:93, 1934.

the clinical manifestations have been brought forward to account for them. The present study was undertaken not only to investigate these changes and to determine if possible the morphologic basis for the profound disturbances of hepatic function which occur under such circumstances, but also to observe the manner in which hepatic recuperation takes place following relief from biliary obstruction.

REPORT OF INVESTIGATION

The autopsy material on which this study is based was obtained from twenty cases of primary carcinoma of the head of the pancreas completely obstructing the common bile duct, in which death followed surgical decompression of the biliary passages. Five of the cases were from the pathologic laboratories of the Pennsylvania Hospital and three from the Lankenau Hospital Research Institute. Dr. John T. Bauer and Dr. Stanley P. Reimann, the respective directors, placed this material at our disposal.

The operative procedures in these cases consisted of cholecystogastrostomy, cholecystoduodenostomy, cholecystostomy or choledochostomy. Pieces of liver for histologic examination were fixed in dilute formaldehyde and Zenker's fluid; a part of the specimen was frozen and sectioned, and the remainder was blocked in paraffin, cut and stained with phosphotungstic acid, hematoxylin-eosin, scarlet red, methylene blue, van Gieson's and Mallory's connective tissue stains, iron-alum-hematoxylin stain, Wilder's [13a] modification of the silver diaminohydroxide stain, Mallory's potassium ferrocyanide stain and McIndoe's [13b] adaptation of the del Rio Hortega silver carbonate stain for biliary canaliculi. In many instances complete sets of serial sections were examined.

The gross changes in the liver, biliary ducts and gallbladder varied considerably depending on the duration of the stasis, the extent of cirrhosis, the type of operative procedure instituted for the relief of the obstruction and the interval following decompression as well as on the presence or absence of metastatic tumor nodules, abscesses, hemorrhages or degenerative hepatic lesions. It would be inappropriate to comment further on these gross changes, the possible combinations of which are so numerous and variable that no single description applies even in the majority of cases. Interest centers particularly on the microscopic changes in the liver.

Pigmentation.—Biliary pigmentation diminished rapidly with the disappearance of granules from the hepatic cells and of the biliary thrombi from the canaliculi and smaller ducts. Pigmentation was still discernible nineteen days after the operation, appearing as a faintly yellowish-staining material which persisted longest in cells nearest the central and sublobular veins and in those isolated by prolongations of connective tissue at the peripheries of the lobules.

Architectural Changes.—Disruption of the intralobular architecture and disorganization and dissociation of hepatic cell cords were constant features, being of mild degree when confined to the inner portions of the lobule (grade 1) and extensive and irregular when involving the middle and outer thirds (grade 2) or the entire lobule diffusely (grade 3). The most marked alterations occurred just beneath the capsule of the liver and in the region of the porta and larger intra-

13a. Wilder, H. C.: Am. J. Path. **8**:785, 1932.

13b. McIndoe, A. H.: Arch. Path. **6**:598, 1928.

hepatic biliary ducts. Both small and large groups of lobules were completely affected in twelve cases; sections from four of these showed uniform disruption of architecture throughout the entire organ (grade 4). The hepatic cells immediately bordering on portal radicles tended to maintain their normal arrangement longest, whereas the remainder were scattered about, lying singly in groups of from three to six or as short isolated cords partially supported by a meshwork of thickened reticular fibers (figs. 1 and 2).

Regressive Changes.—In the majority of cases some degree of regressive change was present in the hepatic cells, the entire parenchyma being involved in some instances (figs. 1 and 2). These changes were characterized chiefly by karyolysis, pyknosis and cytoplasmic disintegration. Necrosis was a constant feature in the inner portions of the lobules (grades 1 and 2), isolated cells being irregularly

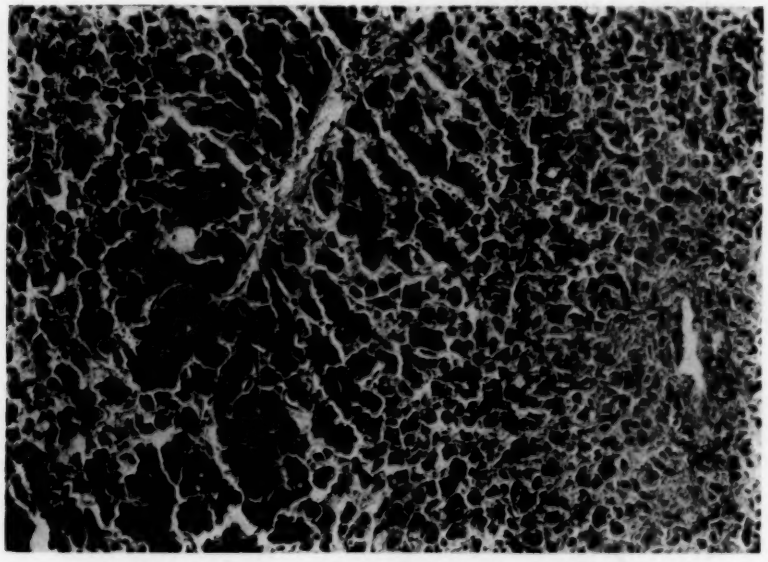

Fig. 1.—Section of the liver. A central vein lies to the right and a portal trinity in the upper left portion of the field. Note the regressive changes in the cells with disorganization and disruption of the hepatic cell cords. Reduced from × 250.

affected in the middle and outer thirds (grades 3 and 4). Certain other cells appeared merely atrophied and distorted, alternating with necrotic cells in the two latter situations. The viable hepatic cells present in areas where disruption and disorganization were particularly well marked varied considerably in size and shape, often presenting bizarre forms resembling lymphocytes and plasma cells. In a few cases many of the cells, especially those about the central and sublobular veins, showed a hyaline type of degeneration, the cytoplasm staining deep red and either being homogeneous or containing hyaline droplets and granules.

A variable feature in half of the cases was the presence of cytoplasmic vacuolation, which appeared most marked just beneath the capsule of the liver, about the central vein (grade 1), or affecting the lobules diffusely in their entirety (grade 2). The vacuoles were usually largest around the central vein and diminished in size toward the periphery where they were minute and numerous and completely

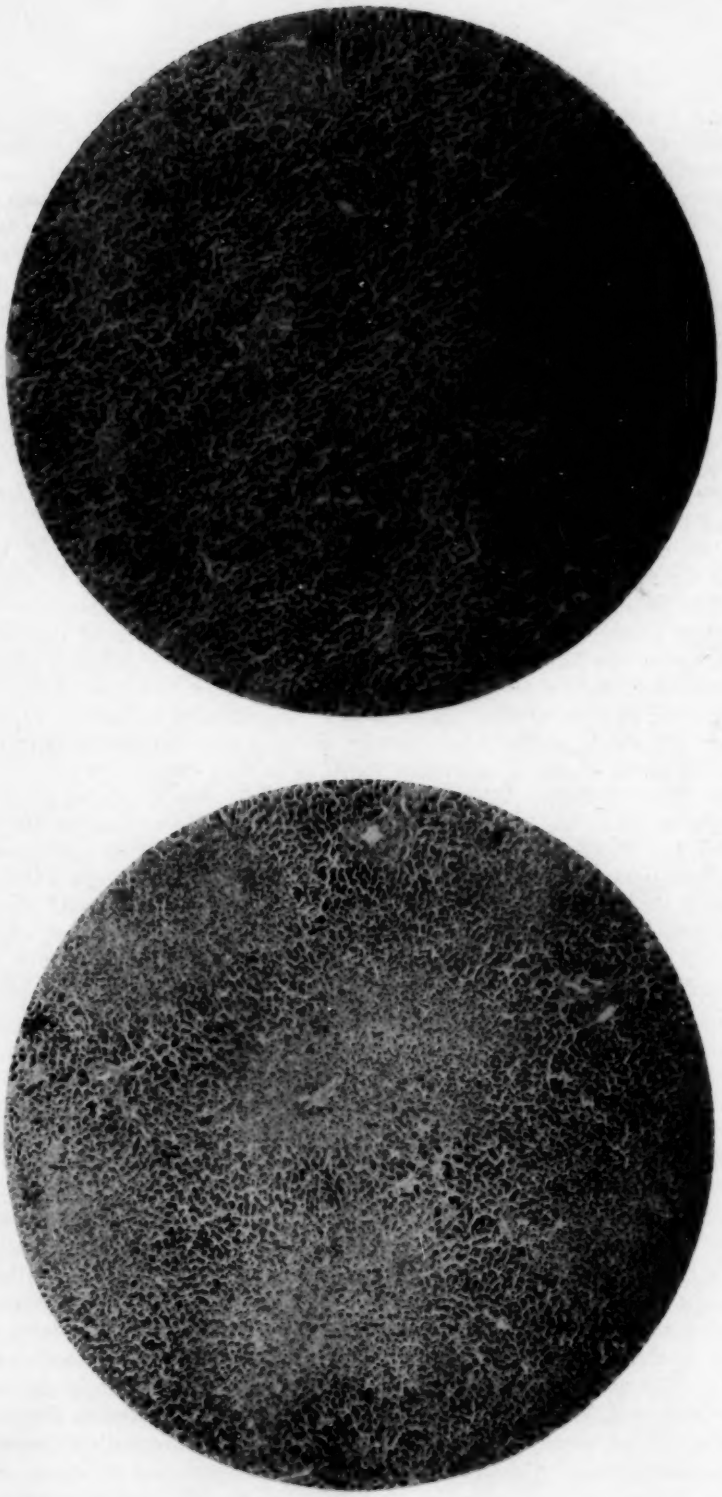

Fig. 2.—Extent of injury to the hepatic cells and disorganization of intralobular architecture; × 40.

replaced the cytoplasm. Biliary pigment was sometimes contained within these vacuoles or concentrated about their circumferences. Hepatic cells isolated by prolongations of connective tissue appeared to have greater difficulty in disposing of their pigment and at times also showed cytoplasmic vacuolation. "Signet ring" forms were uncommon and, rarely, a large vacuole replaced two or three hepatic cells. None of the material was suitably fixed to react with glycogen stains, and only eight gross specimens were available from which to obtain sections to be stained for fat. Although it seems improble that vacuoles of such size and morphology could be interpreted as due to anything but fat, this substance could not be demonstrated by any of the measures employed. It is possible that these vacuoles represented a type of hydropic degeneration. Nuclear vacuolation was present in six cases, occurring indiscriminately within the lobule, usually being inconspicuous and unrelated to cytoplasmic vacuolation. In the development of this phenomenon the chromatin material collected about the nucleolus, which migrated toward the nuclear membrane where it finally became concentrated, leaving the center more or less clear. The nucleus then swelled to two or three times its original size and appeared as a deeply basophilic nuclear ring, within which the nucleolus was sometimes discernible.

Focal midzonal areas of necrosis were present in fourteen cases and were essentially similar to those encountered under ordinary conditions of total biliary stasis. In a few instances the lesions were apparently enlarged as a result of decompression, and in two cases they eventuated in the formation of abscesses. The healing of these necroses appeared to be accomplished exclusively by regeneration and not by organization. Biliary necroses were present in three cases, involving single lobules in their outer thirds or in their entirety or, by extension, several adjacent lobules. When numerous and lying in close approximation to each other, they forced the intervening hepatic cords into more or less parallel rows composed of flattened cells. The pigment was either diffused or transported by phagocytic cells to the periphery of the lesion. No evidence of organization was observed about any of the areas of biliary necrosis. In three cases abscesses were present in relation to the biliary ducts or within biliary or focal midzonal areas of necrosis occupying at times several lobules and showing little evidence of liquefaction in their centers.

Monocytes occasionally seen in mitosis and swollen Kupffer cells containing engulfed pigment, erythrocytes, fragments of necrotic cells and other débris were observed in the sinusoids of many of the specimens. Focal areas of hyperemia were present in fifteen cases, and in these areas the sinusoids were markedly distended and closely packed with well preserved, hemolyzed or conglutinated erythrocytes. Hemorrhage was present in five of these, and the hepatic cells within the areas were atrophied and tended ultimately to disappear. Hyperemia was usually well marked in areas of necrosis, occasionally about the larger intrahepatic biliary ducts, and rarely generalized throughout the section. The accumulation of edema fluid in the perivascular tissue spaces appeared to be a prominent feature tending to compress the sinusoids and to render them bloodless. The sinusoidal reticular walls at times had become ruptured and fragmented in the inner third of the lobule, and rarely, red blood cells extruded into the perivascular tissue spaces. The arteries and arterioles regularly showed an increase in the medial musculature and, less frequently, subintimal proliferation of connective tissue. The branches of the portal vein were usually dilated and their walls thickened by perivascular fibrosis. Although thrombosis of blood vessels was present in several

preparations, it was not attended by infarction nor was it directly associated with necrotic areas in such a manner as to suggest an etiologic relationship.

The smaller biliary ducts which had proliferated while the liver was in a condition of total stasis collapsed following decompression, and their lining cells atrophied and finally vanished. The parietal sacculi tended to reappear in the walls of the larger biliary ducts, the lumens of which contained desquamated epithelial cells, leukocytes, erythrocytes and, in some instances, clumps of bacteria, probably representing an agonal invasion.

In amount and distribution the connective tissue in these livers was similar to that found under conditions of total stasis except that it was apt to be more edematous, was the seat of a greater infiltration of leukocytes and appeared compressed by the regenerating cells at the periphery of the lobule.

Regeneration.—Evidences of cellular regeneration were present in twelve cases and were characterized by nuclear fission and budding and by binucleation and multinucleation of hepatic cells. No mitotic figures were observed in any of the preparations studied. The nuclei in certain regenerating cells became elongated and constricted in the midportion. This indentation, slight at first, penetrated more deeply and resulted ultimately in the separation of the nucleus into two structures of equal size. From other nuclei a bud was formed which gradually enlarged to a size identical with that of the mother nucleus and then separated. Hypertrophic hepatic cells containing single large hyperchromatic nuclei were frequently noted. Regenerating cells were numerous in and about the necrotic areas surrounding the central vein and scattered sporadically either individually or in small groups throughout the lobule. Regenerative changes were seen about the areas of focal midzonal necrosis but not about the biliary necroses. Coincidentally with the formation of new hepatic cells the connective tissue became condensed at the periphery of the lobule. Groups of disorganized cells, in an apparent attempt to reestablish the continuity of the architectural pattern of the liver, put forth short cytoplasmic processes much like pseudopods which, however, often failed to unite with their parent cords. While regeneration of necrotic areas usually proceeded from without inward, it was also observed to occur simultaneously at both the inner and the outer borders of the necroses surrounding the central vein. Reconstruction of the necrotic areas was accomplished not only by regeneration but also by recovery of many of the constituent cells which, although badly damaged, were apparently still viable and capable of returning to normal. Conversely, however, many of the newly regenerated cells had undergone degeneration and necrosis.

Comparative Studies.—As a basis for this study it seemed most desirable to use cases of obstructive jaundice due only to carcinoma of the head of the pancreas. In these cases the condition of the liver and biliary ducts is usually normal prior to the onset of biliary stasis which is regularly complete and permanent until surgical relief is instituted. The influence of biliary stasis on regeneration is hard to evaluate in cases of obstruction of the common duct due to many other causes, in the presence of which it is extremely difficult to eliminate the possibility of previous or coexistent infection. However, the regressive changes in the hepatic cells and the disruption of the architectural pattern seem to be essentially similar in all the cases in which decompression, following biliary stasis, was effectual. These facts were determined by extending the study to include autopsy material from twenty-six additional cases of decompression of the biliary system, the cause of obstruction being carcinoma of the gallbladder (four cases), carcinoma of the duodenum (one case), carcinoma of the common hepatic duct (one case) and calculous cholecystitis (twenty-two cases). Large necrotic areas of obscure etiol-

ogy were present in two of the cases owing to calculous cholecystitis. Of additional particular interest was the presence, in six of these cases, of focal areas of sinusoidal thrombosis varying in size, shape, degree of parenchymal involvement and stage of development. They were usually situated immediately beneath the capsule of the liver and about the central and sublobular veins, being confined to a single or to several adjacent lobules. At first the lesion appeared as an irregularly shaped, poorly demarcated area of hemorrhage, within which could be noted a few isolated atrophied and necrotic hepatic cells. About the borders the sinusoids were hyperemic and the hepatic cells compressed. The red blood cells faded or conglutinated to form small, hyalin-like masses and a fine fibrin network was precipitated and later infiltrated by monocytes and polymorphonuclear leukocytes. Regeneration was well marked in and about these lesions.

COMMENT

If conditions are favorable following decompression the liver may return to a practically normal condition, with or without a variable amount of residual portal fibrosis. Evidence of regeneration may be marked in and about the areas of necrosis surrounding the central vein and in relation to the focal midzonal necroses, as well as sporadically within the lobule and at the periphery. MacMahon [14] observed extremely active regeneration in livers in which the continuity of hepatic cords and biliary capillaries was interrupted and in which biliary pigmentation was present about the somewhat swollen hepatic cells. No statement was made as to whether the cases dealt with were cases of obstruction of the common duct, of decompression or of some form of intrahepatic jaundice. The only reference found relative to hepatic regeneration under conditions of decompression is Bell's [15] work on cholecystogastrostomy on dogs some time following previous ligation of the common bile duct. The rapidity of the regeneration depended roughly on the damage to be repaired and on the duration of the obstruction, usually being completed in from two to four months.

We were unable to find mitotic figures in the livers of any of our patients, but, in view of the opinions of others (Fishback [16] and MacMahon) with regard to hepatic regeneration, this may be of little significance, for figures indicative of mitotic division resulting in the formation of two or more nuclei in a single cell may have escaped observation. Rössle [17] was convinced that amitosis could play no rôle in the growth of tissue, and Doljanski [18] stated that he never saw a cell form in tissue cultures of the liver from which he could conclude

14. MacMahon, H. E.: Ztschr. f. mikr.-anat. Forsch. **32**:413, 1933.
15. Bell, L. P.: California & West. Med. **25**:503, 1926.
16. Fishback, F. C.: Arch. Path. **7**:955, 1929.
17. Rössle, R.: Handbuch der normalen und pathologischen Physiologie, Berlin, Julius Springer, 1927, vol. 14, p. 923.
18. Doljanski, L.: Arch. f. exper. Zellforsch. **11**:261, 1931.

that amitosis contributed to the multiplication of cells. However, recent investigators emphasize the importance of amitosis (Clara,[19] and MacMahon) with cytoplasmic division probably lagging behind (Schultz, Hall and Baker),[20] the number of binuclear cells being finally reduced to normal as a result of a prompt division of the hepatic cells in a series of crops (Ponfick).[21] An interesting question, as stated by Fishback, concerns the extent of participation of biliary ducts in the regeneration of hepatic cells. Marchand,[22] Ribbert [23] and Muir [24] stated that they found no proliferation of biliary ducts in the livers of human beings; they attributed the apparent proliferation to either degeneration or regeneration and rearrangement of the hepatic cells in an attempt to preserve their continuity. Meder,[25] Carraro,[26] Stroebe,[27] Barbacci,[28] MacCallum,[29] K. Hess,[30] O. Hess,[31] Miller and Rutherford [32] and Herxheimer and Gerlach,[33] on the contrary expressed a belief that biliary ducts do proliferate and, with the exception of Carraro, these authors thought that biliary ducts may serve as a source of new hepatic cells, at least under conditions of stress. They found the first evidence of regenerative activity to be present in the proliferating cells of the biliary ducts. Lieber and Stewart [34] found no regenerating hepatic cells in the livers of patients with complete and permanent stasis, despite the excessive and progressive proliferation of biliary ducts. In autoplastic hepatic transplants Cameron and Oakley [35] demonstrated that the hepatic cells and epithelium of the biliary ducts grow independently and show no tendency to unite with each other. As a result of the present study no evidence is adduced that following decompression the biliary ducts act as a source for the formation of new

19. Clara, M.: Ztschr. f. mikr.-anat. Forsch. **22**:145, 1930; **26**:45, 1931.
20. Schultz, E. W.; Hall, E. M., and Baker, H. V.: J. M. Research **44**:207, 1923.
21. Ponfick, E.: Virchows Arch. f. path. Anat. **230**:289, 1921.
22. Marchand, F.: Beitr. z. path. Anat. u. z. allg. Path. **17**:206, 1895.
23. Ribbert: Arch. f. Entwcklngsmechn. d. Organ. **18**:267, 1904.
24. Muir, R.: J. Path. & Bact. **12**:287, 1908.
25. Meder, E.: Beitr. z. path. Anat. u. z. allg. Path. **17**:143, 1895.
26. Carraro, A.: Virchows Arch. f. path. Anat. **195**:462, 1909.
27. Stroebe, H.: Beitr. z. path. Anat. u. z. allg. Path. **21**:379, 1897.
28. Barbacci, O.: Beitr. z. path. Anat. u. z. allg. Path. **30**:49, 1901.
29. MacCallum, W. G.: Bull. Johns Hopkins Hosp. **10**:375, 1902.
30. Hess, K.: Virchows Arch. f. path. Anat. **121**:154, 1890.
31. Hess, O.: Beitr. z. path. Anat. u. z. allg. Path. **56**:22, 1913.
32. Miller, J., and Rutherford, A.: Quart. J. Med. **17**:81, 1923.
33. Herxheimer, G., and Gerlach, W.: Beitr. z. path. Anat. u. z. allg. Path. **68**:93, 1921.
34. Lieber, M. M., and Stewart, H. L.: Arch. Path. **17**:362, 1934.
35. Cameron, G. R., and Oakley, C. L.: J. Path. & Bact. **38**:17, 1934.

hepatic cells. Indeed, under such circumstances, the regeneration of hepatic cells progresses rapidly, whereas the newly proliferated biliary ducts are undergoing involution. Furthermore, a large number of regenerating hepatic cells are present well within the lobule, distinctly separated from the biliary ducts by a zone of hepatic parenchyma at the periphery.

The material at our disposal was unsuited to the study of the hepatic changes dependent on the effects of a long continued anastomosis between the biliary tract and some portion of the gastro-intestinal tract. The experimental data pertaining to this condition in animals will be referred to later. In patients coming to autopsy shortly after decompression, the parenchyma of the liver was frequently extensively disorganized and degenerated, the regressive changes occasionally progressing to acute diffuse hepatic necrosis. It is not possible to compare these changes with those of acute yellow atrophy of the liver, since there is no unanimity of opinion as to the early picture of the latter lesion (Roman).[36] It would have been interesting to investigate the relationship between the effects of these destructive changes and the mechanism of jaundice, but, in this series of cases, functional studies following operation were unfortunately too meager to permit such a study. Available data indicate that, as a rule, the hyperbilirubinemia and clinical manifestations of jaundice steadily decrease in patients who recover following a release of biliary obstruction. Weir and Walters,[13] however, pointed out that a slow decline or a rise of bilirubin in the serum postoperatively indicates serious and progressive hepatic parenchymal injury. It has long been recognized (Judd and Lyons,[37] and Walters and Parham [7]) that if the draining bile becomes thin, pale and increased in volume the import is serious and indicates failing hepatic function. Walters, Greene and Frederickson [38] found that in patients with marked cholerrhagia following decompression, the concentration and total output of bilirubin were reduced and the characteristic constituents of the bile were practically entirely lacking, even though this deficient secretion was elaborated in considerable quantity. The regressive morphologic observations in certain of our cases permit the theory that the hepatic excretion of biliary pigment may be seriously impaired following operation, when the factor underlying the production of jaundice changes from an extrahepatic obstruction to an intrahepatic lesion, probably similar in all respects to that characteristic of acute diffuse necrosis (acute yellow atrophy of the liver).

36. Roman, B.: Arch. Path. **4**:399, 1927.

37. Judd, E. S., and Lyons, J. H.: Ann. Surg. **77**:281, 1923.

38. Walters, W.; Greene, C. H., and Frederickson, C. H.: Ann. Surg. **91**:686, 1930.

This prevailing and characteristic picture of extensive necrosis in combination with hepatic parenchymal dissociation apparently does not occur with any degree of frequency in conditions other than surgical decompression following total stasis. This conclusion is supported by observations made on a control series comprising twenty-four cases of total stasis due to carcinoma of the head of the pancreas without decompression and on thirteen instances of cholecystectomy or cholecystostomy in nonjaundiced patients with calculous cholecystitis. We also examined many livers obtained from patients dying as a result of a variety of conditions unrelated to the liver, gallbladder or biliary ducts, some of whom had been subjected to prolonged anesthesia. One of the control cases is of great significance. A patient with obstructive jaundice due to carcinoma of the common hepatic duct was subjected to cholecystogastrostomy which, of course, did not relieve the biliary stasis. He died eighteen hours following operation. The histologic preparations of the liver showed the typical picture of total stasis with complete absence, however, of the combined regressive changes in the cells and disruption of intralobular pattern so characteristic of the liver in cases of decompression as described. The assumption appears to be justified, therefore, that this picture is due not directly to prolonged anesthesia or operative procedures on the biliary tract, but to certain factors associated with decompression of an obstructed biliary system.

During total biliary stasis the hepatic blood pressure rises in an attempt to maintain adequate function of the hepatic cells in the face of the gradually increasing pressure which acts as an obstacle to the secretion or excretion of bile. The combination of acute dilatation of intrahepatic blood vessels occurring simultaneously with decompression of a hydrohepatotic liver results in sudden and marked alterations in pressure. The rapidity of induction of the changes may be one of the factors responsible for the production of marked parenchymal disorganization and may also account in part for the distention of sinusoids with corresponding atrophy of hepatic cell cords, edema of the perivascular tissue spaces, and fraying and tearing of sinusoidal reticular walls, particularly since the last mentioned lesions are most marked about the larger intrahepatic ducts where the effects of this force are probably greatest. Hemorrhage into the biliary conducting system may also be due to this sudden release in intraductal pressure, especially in patients with a hemorrhagic tendency already established. It is difficult to evaluate the importance of this factor in the production of widespread degeneration and other regressive changes, but pressure, as is well known, is a common cause of necrosis.

The chemical characteristics of the bile following the release of an obstruction of a common duct have been studied by a number of investi-

gators (von Czyhlarz, Fuchs and von Fürth,[39] Chabrol, Benard and Bariety,[40] Rosenthal, von Falkenhausen and Freund,[41] Greene, Walters and Frederickson,[42] Ravdin, Johnston, Riegel and Wright[43]). The formation of biliary acids, which may be partially or completely inhibited during total stasis, returns to normal relatively rapidly following decompression, if the liver has been not too seriously injured. Ravdin and his co-workers found a low calcium content and a high chloride level, which tended to fall in patients who recovered and to increase in those who died. The biliary salts were constantly absent in the liver bile when the common duct had been completely obstructed for a week or more, and they reappeared only after a variable period of from one to four weeks. The relationship which these chemical disturbances bear to the morphologic changes in the liver in cases such as we have described is at present unknown, although it seems logical to assume that the delayed reappearance of bile acids in the bile following decompression may be partly the direct result of the hepatic disorganization and regressive changes.

There is abundant experimental evidence to suggest that the creation of a biliary fistula or of an anastomosis between the gallbladder and any part of the gastro-intestinal tract is regularly attended by infection of the biliary passages and the liver (Gatewood and Poppens,[44] Lehman,[45] Horsley,[46] Beaver,[47] Gatewood and Lawton,[48] Gage[49] and Wangensteen[50]). The experience of Walters, Greene and Frederickson[38] with dogs with permanent biliary fistulas indicates that the development of cholangitis with associated cirrhotic changes in the liver may rapidly reduce the quantity of bile acids in the bile. The importance of infection as a serious complication in our cases of shorter duration is attested by the presence of fresh inflammatory changes in

39. von Czyhlarz, E.; Fuchs, A., and von Fürth, O.: Biochem. Ztschr. **49**: 120, 1913.

40. Chabrol, E.; Benard, H., and Bariety, H.: Bull. et mém. Soc. méd. d'hôp. de Paris **50**:992, 1926.

41. Rosenthal, F.; von Falkenhausen, M., and Freund, H.: Arch. f. exper. Path. u. Pharmakol. **111**:170, 1926.

42. Greene, C. H.; Walters, W., and Frederickson, C. H.: J. Clin. Investigation **9**:295, 1931.

43. Ravdin, I. S.; Johnston, C. G.; Riegel, C., and Wright, S. L.: J. Clin. Investigation **12**:659, 1933.

44. Gatewood, E. T., and Poppens, P. H.: Surg., Gynec. & Obst. **35**:445, 1922.

45. Lehman, E. P.: Arch. Surg. **9**:16, 1924.

46. Horsley, J. S.: South. M. J. **20**:669, 1927.

47. Beaver, M. G.: Arch. Surg. **18**:889, 1929.

48. Gatewood, E. T., and Lawton, S. E.: Surg., Gynec. & Obst. **50**:40, 1930.

49. Gage, I. M.: Proc. Soc. Exper. Biol. & Med. **28**:693, 1931.

50. Wangensteen, O. H.: Ann. Surg. **87**:54, 1928.

and about the larger ducts, in association with the biliary and focal midzonal areas of necrosis and elsewhere in the hepatic parenchyma in relation to the portal radicles and terminal biliary ducts. These lesions are probably the result of an ascending infection and may contribute to the production of vascular thrombosis and acute regressive changes in the liver.

SUMMARY

Following surgical decompression of an obstructed biliary system, hepatic pigmentation diminishes progressively in patients who survive the immediate effects of the operation, and the hepatic parenchyma tends to return to an approximately normal condition. This is accomplished by the recovery of many of the degenerated but still viable hepatic cells and also by regeneration. The latter is characterized by nuclear fission and budding and by binucleation and multinucleation of hepatic cells, without the appearance of mitotic figures. There is no evidence that hepatic cells arise from the biliary ducts, which rapidly involute following decompression. Lobular expansion subsequent to regeneration of hepatic cells results in compression and condensation of connective tissue at the periphery. The features of regeneration may be minimal or entirely absent in some livers in which the changes are those of a severe acute hepatosis occasionally complicated by hemorrhage and superimposed infection. Disruption of the intralobular architecture with disorganization and dissociation of hepatic cell cords occurs regularly. The necrosis in the inner third of the lobule often extends into the middle and outer thirds or involves the entire lobule, resulting occasionally in acute diffuse necrosis. Many of the focal midzonal and biliary necroses also enlarge and may form abscesses. In addition, the hepatic cells may be atrophied and distorted and at times show cytoplasmic and nuclear vacuolation. The recently regenerated hepatic cells may undergo degeneration and necrosis. The vascular changes include thrombosis, rupture of the sinusoidal reticular walls, hemorrhage, edema of the perivascular tissue spaces and hyperemia, either focal or general throughout the organ. Physical, chemical and infectious factors probably play an etiologic rôle in the pathogenesis of these lesions.

CYTOLOGY OF PERITONEAL FLUID IN PARTIALLY HEPATECTOMIZED ANIMALS

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The cells of the peritoneal fluid have been the object of frequent and extensive studies ever since von Recklinghausen [1] studied the routes of absorption of materials injected into the peritoneal space. The literature is too extensive to review in this report, and the reader is referred to the rather complete review given by Webb.[2]

Earlier studies of these cells were concerned with their reaction to various substances injected into the peritoneum. Other studies were concerned with the genetic relationships of these cells to those of the blood stream, and still others with the origin of the cells of serous exudates in general. Cellular continuity and transformations in various inflammatory reactions have been extensively studied. The relation of these cells to immunity and their mobilization and transfer to other parts of the body in defense reactions have been followed.

More recently, in studies directed toward the protection of the peritoneum against infection, further interest has been centered on the cytologic character of the protective mechanism. Various vaccines administered prior to operation in the lower portion of the abdomen induce a protective effect which materially lowers the incidence of postoperative peritonitis.[3] Bargen [4] and his co-workers have found this procedure useful, and reported the results of the clinical applications of the method. The cytologic response to these vaccines is now being investigated, and Rixford[5] recently made a preliminary report on this work. Steinberg and Goldblatt[6] reported an experimental study on dogs in which peritoneal vaccination was carried out by the

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From the Division of Experimental Medicine, the Mayo Clinic.

1. von Recklinghausen, F.: Virchows Arch. f. path. Anat. **26**:172, 1863.
2. Webb, R. L.: Am. J. Anat. **49**:283, 1931.
3. Rankin, F. W., and Bargen, J. A.: Arch. Surg. **22**:98, 1931.
4. Bargen, J. A.: Proc. Staff Meet., Mayo Clin. **8**:581, 1933.
5. Rixford, E. L.: Proc. Staff Meet., Mayo Clin. **8**:586, 1933.
6. Steinberg, Bernhard, and Goldblatt, Harry: Surg., Gynec. & Obst. **57**:15, 1933.

injection of a suspension of dead organisms in a solution of tragacanth. A marked increase in the total cell count to 153,000 per cubic millimeter of peritoneal fluid was observed within ten hours. Differential cell counts were not recorded, although the authors regarded the polymorphonuclear neutrophil as the predominant cell for the first forty-eight hours, after which there was an appreciable increase in the number of the mononuclear cells. Control data on both the total and the differential peritoneal cell count prior to the injection of the vaccine would facilitate the interpretation of these results.

This report is concerned with changes induced in the total and differential peritoneal cell count in animals from which a considerable portion of the liver had been removed. Recently, one of us (Montgomery [7]), in a study of the peritoneal cells of various laboratory animals, demonstrated that the total number of cells per cubic millimeter of fluid in the white rat was normally in excess of 100,000. This was an advance over the previous work on this subject, which had concerned itself with the determination of percentages only and suggested the work which is now being reported. Using the technic described previously, it was possible to determine, within the limits of error, the number of cells per cubic millimeter in the peritoneal fluid of animals. Since these cells increase enormously in the presence of various irritants and, furthermore, since they migrate to other regions of the body to combat infections, we were interested to know the effect of surgical intervention in the upper portion of the abdomen on the number of cells per unit of fluid in the peritoneal space. Partial removal of the liver, which is readily accomplished in rats, was selected as the operative procedure. The liver, of course, was not considered a source for these exudative cells, but we believed that the operation incident to its removal might not be without effect. The white rat was selected for the study.

PROCEDURE

Ten healthy male white rats, 6 months of age and weighing between 200 and 225 Gm., were selected for this study. They were in good physical condition, so far as could be determined. To secure adequate control data, five samples of peritoneal fluid were taken from each animal during three weeks prior to the operation. Both total and differential cell counts were made on these fluids. The smears were stained with Wright's stain, and 200 cells were counted from each smear. From five of the animals about 75 per cent of the liver was removed aseptically by a technic described in a previous article.[8] In three animals none of the liver was removed, but a small portion of one lobe was excised and transplanted into the peritoneal space. This served as a control for the hepatectomized

7. Montgomery, L. G.: Proc. Staff Meet., Mayo Clin. **7**:589, 1932.
8. Higgins, G. M., and Anderson, R. M.: Arch. Path. **12**:186, 1931.

group, in which a small remnant of hepatic tissue always remained adjacent to the level of the ligature. In two of the rats simple laparotomy alone was performed. Samples of blood and peritoneal fluid were taken on the third day after operation and at frequent intervals thereafter for ten weeks.

RESULTS

Since the morphology of the cells of the peritoneal fluid of the white rat has been adequately described, we shall restrict our consideration to an analysis of the total and relative number of cells present before and after partial hepatectomy.

On the basis of the fifty control counts that were made on the ten animals prior to operation, a mean total cell count of 127,360 ± 9,150 per cubic millimeter of peritoneal fluid was determined. There was

TABLE 1.—*Total Number of Peritoneal Cells per Cubic Millimeter Before Operation (Control Counts)*

Animal	Total Number of Cells (Average of Five Counts)*
1	108,400 ± 17,100
2	82,900 ± 4,600
3	147,300 ± 9,300
4	84,400 ± 8,000
5	99,300 ± 6,200
6	205,300 ± 6,500
7	190,300 ± 11,500
8	149,800 ± 6,600
9	116,400 ± 7,900
10	94,500 ± 7,100

* The average for the entire series (50 counts) was 127,360 ± 9,150.

a wide variation in the mean total cell count of the peritoneal fluid of the individual animals (table 1). The lowest mean count recorded was 82,900 ± 4,600, and the highest, 205,300 ± 6,500. It will be noted from this table that the probable errors, except in the case of animal 1, were not large, and thus there was considerable regularity in the counts determined. In rats with a high peritoneal cell count the count remained consistently high, and in those with a lower count it remained consistently low, during the period in which control counts were taken. These differences are significant statistically, but we offer as yet no explanation why counts for one animal should be double those found for another. We believe that the variation may be correlated, however, with the presence of absorptive phenomena in the peritoneum.

The differential peritoneal cell counts, on the other hand, revealed more uniformity for the whole group. We did not attempt to distinguish the clasmatocytes from the monocytes and large lymphocytes, but placed them in one group designated as mononuclear cells. The

small lymphocytes were classified as lymphocytes. The eosinophilic leukocytes were easily identified, as were the large mast cells. We noted only a small percentage of polymorphonuclear neutrophils in our series, which indicated that a pathologic condition may have existed, for it is generally conceded that these cells do not occur in serous fluids unless infection is present. This condition was transient, however, for soon after recovery from the operation neutrophils were not observed in the smears.

The average differential count of the 10,000 cells which served as a control is shown in table 2. Our figures agree essentially with those

TABLE 2.—*Percentage of Peritoneal Cells in All Ten Animals Prior to Operation, (Fifty Counts, 10,000 Cells)*

	Per Cent
Mononuclears	56.90 ± 0.67
Lymphocytes	3.94 ± 0.24
Eosinophils	32.12 ± 0.78
Neutrophils	4.20 ± 0.67
Mast cells	2.82 ± 0.16

TABLE 3.—*Total Number of Peritoneal Cells per Cubic Millimeter After Partial Removal of the Liver*

Time After Operation	Average Count (Five Animals)
3 days	10,250 ± 1,190
5 days	10,370 ± 750
14 days	17,600 ± 3,100
28 days	39,600 ± 4,600
42 days	61,000 ± 8,500
56 days	69,800 ± 7,800
4 months	29,800 ± 2,000

of Webb, except that he did not encounter neutrophils in his smears and found a much larger mast cell count (7.36 ± 0.38 per cent). The lowest mean percentage of mononuclear cells recorded for any animal was 52.84 ± 1.03, and the highest, 62.30 ± 1.70. The difference, together with its probable error, is 9.46 ± 1.98, indicating that there is a slight significant difference between these two percentages.

In the animal in which the mononuclear count was low the lymphocyte count was also low, but the eosinophilic leukocyte count was high. Accordingly, in these groups the difference between the high and low differential counts was about four times the probable error of the difference, thus bordering on the significant. We believe, however, that the figures in table 2 represent fairly well the control data prior to operation.

The data assembled from the total peritoneal cell counts after partial hepatectomy have been condensed into table 3, and the data obtained from the control group in which simple laparotomy or laparotomy with implantation of liver was performed have been condensed into table 4. It is observed that, on the third postoperative day, the mean count recorded for the five animals from which the liver had been removed had fallen to 10,250 ±1,190 (table 3), whereas the count for the five control animals was 129,300 ± 20,000 (table 4). There was no essential difference between the preoperative and postoperative counts in control animals from which the liver had not been removed, whereas a marked fall from a mean of 127,360 to one of 10,250 occurred in the animals subjected to partial removal of the liver. It was evident, too, that there was no effect on the number of peritoneal cells in the fluid of animals that had had autogenous implants of liver into the peritoneum.

TABLE 4.—*Total Number of Peritoneal Cells per Cubic Millimeter After Laparotomy and Implanting Small Portion of Liver into Peritoneum*

Time After Operation	Average Count (Five Animals)
3 days	129,300 ± 20,000
5 days	134,000 ± 16,000
14 days	173,100 ± 9,500
28 days	123,400 ± 13,000
42 days	151,800 ± 20,500
56 days	160,100 ± 13,500
4 months	136,300 ± 6,200

The postoperative total cell count appeared to bear no relation to the level of the preoperative count; the mean control count of 147,300 ± 9,300 (table 1) in animal 3 dropped on the third day after operation to 4,500 per cubic millimeter, whereas the lower initial control cell count of 84,400 ± 8,000 in animal 4 dropped to only 14,000. The mean peritoneal cell count, taken at intervals during recovery and restoration of the liver, remained low and never fully regained the level established as the preoperative control count. The mean total count taken four months after operation—29,800 ± 2,000—was exceedingly low and indicated that great variation from the normal peritoneal cell count might be expected in animals in which the restored liver had assumed special relations somewhat different from those of the normal organ. The data of postoperative cell counts for the control series (table 4) revealed no marked deviation from the preoperative control levels. The counts, as a rule, were higher than the mean preoperative control count, but there were no marked changes such as were found in the animals from which the liver had been removed.

The differential peritoneal counts during the postoperative period did not vary greatly from the control (fig. 1), except the polymor-

phonuclear neutrophil counts, which, during the first three days after operation, rose to a percentage of 25.00 ± 3.81. The percentage of mast cells remained the same, whereas the percentage of mononuclear leukocytes and eosinophils dropped to 35.40 ± 4.56 and 26.80 ± 4.12,

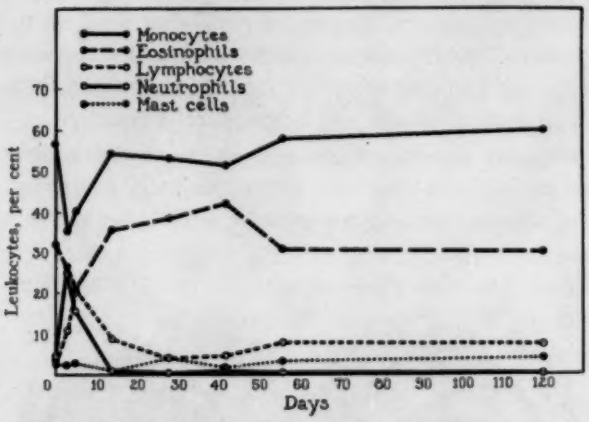

Fig. 1.—Differential peritoneal cell count after partial removal of the liver.

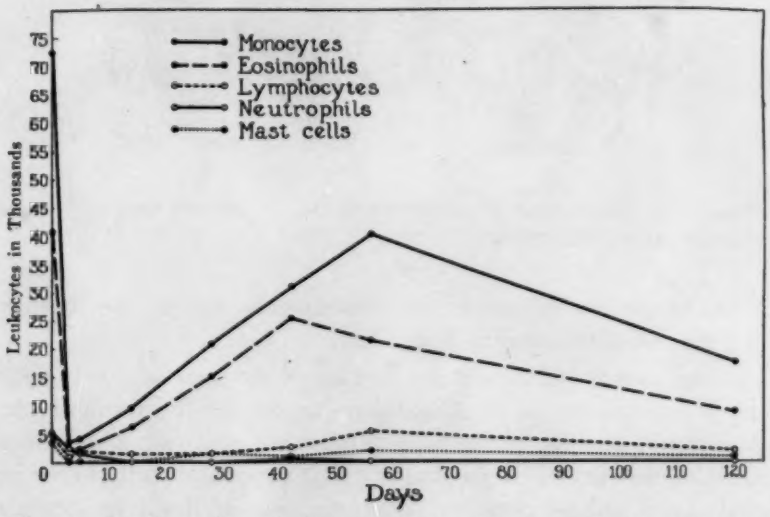

Fig. 2.—Total number of different kinds of peritoneal cells after partial removal of the liver.

respectively. Computing the number of cells present on the basis of the differential count (fig. 2), it appears that the mononuclear cells had dropped from 72,000 to 3,000, the eosinophils from 40,000 to 2,000 and the mast cells from 3,500 to 2,300. Although the percentage of

neutrophils had increased greatly, the actual number of neutrophils had fallen from 5,300 to 2,600 during the three day period. On the fourteenth day after operation a more nearly normal relative distribution of cells was restored, although the mean total cell count was low —17,600 ± 3,100. Although there was a gradual increase in the total number of cells per cubic millimeter of peritoneal fluid up to the eighth week, the relative distribution remained essentially unchanged. This would seem to indicate that whatever factors determined the cell content of the peritoneal fluid affected all types of cells equally.

There were no significant changes in the relative distribution of the cells in the fluid of the five control animals following operation. There was a transient rise in eosinophilic leukocytes and a correspond-

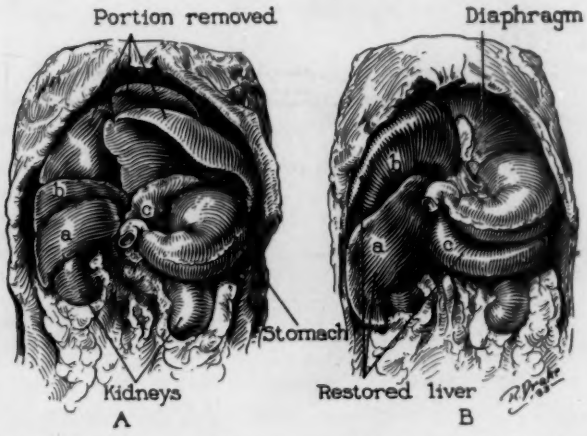

Fig. 3.—*A*, normal liver in peritoneum of rat; *B*, restored liver in peritoneum of rat after partial hepatectomy.

ing fall in the percentage of mononuclear cells, but by the fourteenth day a normal distribution was regained.

In the normal rat the convex surface of the liver is closely applied to the serosal surface of the diaphragm (fig. 3A). As a result of partial hepatectomy, whereby entire hepatic lobes are removed, a considerable portion of the surface of the diaphragm is exposed directly to the peritoneal cavity and its contents. As restoration of the liver occurs and the three small remaining hepatic lobes greatly increase in size, the surface of the diaphragm is again partially covered by the encroaching liver. However, even when restoration is complete and a liver equal to or greater than the normal has been restored, a considerable segment of the diaphragm remains in more or less direct continuity with the peritoneal space (fig. 3B). These changes in the spatial relations of

the diaphragm and liver following partial hepatectomy and the consequent restoration of the liver may explain the low peritoneal cell counts which we obtained. The diaphragm is the organ through which absorption from the peritoneal space most readily occurs. We are certain that these low cell counts are not due to factors of dilution.

SUMMARY

A study of the cells of the peritoneal fluid of the albino rat was made to determine the effect of partial hepatectomy on the total number of these cells and their differential relationships. It was found that a marked decrease in the total number of the cells occurred, whereas no significant change was found in the relative numbers of the different types. In a control group of animals in which simple laparotomy was performed, either with or without implantation of hepatic tissue into the peritoneal cavity, significant changes were not found.

PHAGOCYTIC BEHAVIOR OF INTERSTITIAL CELLS OF BRAIN PARENCHYMA OF ADULT RABBIT TOWARD COLLOIDAL SOLUTIONS AND BACTERIA

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With the separation by Rio-Hortega [1] of the third element of Cajal into two groups, the microglia and the oligodendroglia cells, believed by him to possess distinct functional, morphologic and staining properties and a separate origin, the modern knowledge of these cells may be said to have begun. Hortega concluded that not only do the microglia cells possess the two properties essential for the proper functioning of a macrophage, viz., mobility and phagocytosis, but collectively they represent broadly the so-called reticulo-endothelial system locally in the brain. In spite of his investigations and those of his pupils, there still exists a controversy as to whether the microglia cells are the sole source of cerebral macrophages or whether the latter have a double origin from microglia cells and astrocytes. Only a few experiments have been conducted to demonstrate the phagocytosis of vital dyes by microglia cells, and none have been made on the behavior of these cells toward bacteria. The discrepancies in the results obtained by different workers are due primarily to inadequate technic or to differences in interpretation. Since the storage of true colloidal solutions and bacteria is unquestionably bound up with the process of phagocytosis, these can be employed to determine the phagocytic properties of the various interstitial cells of the rabbit's brain.

REVIEW OF THE LITERATURE

Testa,[2] Cavallaro [3] and Gozzano [4] demonstrated ingested vital dyes in microglia cells. By the use of gum arabic to weaken the intensity of silver impregnation, Bolsi [5] noted granules of trypan blue in microglia cells. Russell [6] observed the affinity of transitional microglia cells for trypan blue in incompletely impregnated and toned sections of aseptically

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1. del Rio-Hortega, P.: Arch. de neurobiol. **11**:212, 1921.
2. Testa, M.: Folia med. **14**:725, 1928.
3. Cavallaro, V.: Pathologica **19**:11, 1927.
4. Gozzano, M.: Riv. di neurol. **1**:377, 1928.
5. Bolsi, D.: Riv. di pat. nerv. **37**:1, 1931.
6. Russell, D.: Am. J. Path. **5**:451, 1929.

injured cerebral tissue of rabbits. I found that the exact repetition of Russell's technic yielded, in general, unsatisfactory results, for not only were the cytoplasmic microglial processes very coarsely granular but they could not always be distinguished with certainty from the similarly coarse granular elements of the ground substance. Beletzky and Garwaki [7] observed the adsorption of ferric saccharate by mesoglia cells, but they did not state whether the ferric saccharate was in a true colloidal state; this is unfortunate, for it is well known that there are samples of saccharated or nonsaccharated oxide of iron which yield clear brown solutions free from suspended particles. Bratianu and Llombart [8] stated that the microglia cells do not possess the power of "fixing" colored colloidal solutions either in the normal or in the pathologic state and that macrophages arise not only from microglia cells but from oligodendrocytes and adventitial cells as well.

In spite of their close resemblance to macrophages in tissue cultures, Costero [9] claimed to have cultivated microglia cells in vitro from the brains of from 2 to 3 month human embryos, of from 7 to 20 day chick embryos and of new-born guinea-pigs and to have demonstrated the capacity of these cells for ingesting lithium carmine. Wells and Carmichael [10] observed in sections of cultures of embryo chick brains specifically impregnated for microglia cells wandering cells interpreted by them as being similar to microglia cells and capable of taking up in vitro neutral red and trypan blue. Mihálik [11] likewise noted in chick embryo brain cultures migrating and wandering cells which he identified as macrophages and as the third element of Cajal. It is evident, therefore, that until microglia cells of unquestioned identity are grown in vitro, preferably, if possible, in tissue culture consisting only of these cells, it is idle to speak of the phagocytic power of microglia cells for vital dyes in vitro.

On the basis of purely morphologic observations, the view has long been advanced that neuroglia cells are capable of producing macrophages (Merzbacher,[12] Alzheimer,[13] Creutzfeldt and Metz [14]). Alz-

7. Beletzky, W., and Garwaki, N.: Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:474, 1931.

8. Bratianu, S., and Llombart, A.: Ann. d'anat. path. **62**:849, 1929.

9. Costero, I.: Ztschr. f. d. ges. Neurol. u. Psychiat. **132**:371, 1931.

10. Wells, A. Q., and Carmichael, E. A.: Brain **53**:1, 1930.

11. Mihálik, P.: Anat. Rec. **54**:157, 1932.

12. Merzbacher, L., in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1909, vol. 3, p. 1.

13. Alzheimer, A., in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1921, vol. 3.

14. Creutzfeldt, H. G., and Metz, H.: Ztschr. f. d. ges. Neurol. u. Psychiat. **106**:18, 1926.

heimer termed the macrophages derived from any type of astrocyte "ameboid glial cells." Later, Rosenthal [15] interpreted these cells as a type which suffered regressive changes and denied to them any phagocytic properties. Rio-Hortega and Penfield [16] observed no suggestion of the transformation of astrocytes into macrophages at the borders of experimental cerebral traumatic lesions in rabbits.

Nevertheless, this classic theory still attracts many adherents. Creutzfeldt and Metz [14] concluded after a study of fixed sections of diseased human cerebral tissue that the astrocytes contribute in part to the formation of macrophages. However, they differed from Alzheimer, who stated that the phagocytic function was common to all types of glial cells in maintaining that mobile macrophages originate from microglia cells and fixed macrophages from astrocytes. This concept of a fixed scavenger cell is not entirely acceptable in that it denies to the cells one of the two fundamental properties requisite for their function, the power of locomotion.

Even the application to this problem of vital staining and tissue cultures has led to contradictory results. Thus Goldmann [17] in his pioneer study of vital staining of the central nervous system observed more or less diffuse coloring of the astrocytes after cerebral subarachnoid injection of trypan blue in rabbits. Aside from the obvious fact that he was dealing with injured or dead cells, his observations must be discounted because of the complicating toxicity of the dye, as indicated by the fact that the initial injection was followed by an immediate reaction consisting of muscular spasms, convulsions and coma and death occurred nine hours later. Rachmanow [18] and Macklin and Macklin [19] observed storage of trypan blue in astrocytes about cerebral injuries in rabbits and rats, respectively. Mandlestamm [20] concluded that astrocytes "activated" by trauma are well stained by trypan blue. Recently, Roussy, Lhermitte and Oberling [21] claimed to have demonstrated trypan blue granules in astrocytes in rabbit brains directly exposed to radium. They evidently ignored one of the accepted signs of life, death or injury of the cell, for clearly the astrocytes represented in figure 12 of their article are either dead or injured, as shown by the diffuse or granular trypan blue

15. Rosenthal, S., in Nissl, F., and Alzheimer, A.: Histologische und histopathologische Arbeiten über die Grosshirnrinde, Jena, Gustav Fischer, 1913, vol. 6, p. 69.

16. del Rio-Hortega, P., and Penfield, W.: Bull. Johns Hopkins Hosp. **41**:278, 1927.

17. Goldmann, E. E.: Abhandl. d. k. Preus. Akad. d. Wissensch., 1913.

18. Rachmanow, A.: Folia neuro-biol. **7**:750, 1913.

19. Macklin, C. C., and Macklin, M. T.: Arch. Neurol. & Psychiat. **3**:353, 1920.

20. Mandlestamm, A.: Ztschr. f. d. ges. exper. Med. **62**:471, 1928.

21. Roussy, G.; Lhermitte, J., and Oberling, C.: Rev. neurol. **1**:878, 1930.

staining of both the cytoplasm and the nuclei. Hence, they were not dealing with a true phagocytic process, and their observation is not valid. Furthermore, Russell,[6] Bolsi [5] and Bratianu and Guerriero [22] were unable to confirm their observations in respect to astrocytes in either traumatic or experimentally induced lesions in the rabbit's brain. Verne [23] observed in the second phase in the life of cultures of nerve tissue from 6 to 10 day chick and rat embryos emigrating cells interpreted as neuroglia cells which had the power of ingesting lithium carmine in vitro and of transforming themselves into macrophages. Examination of his drawings compels the conclusion that these "neuroglia cells" closely resemble true macrophages and are probably true wandering cells.

Pruijs,[24] Ferraro and Davidoff [25] and Cramer and Alpers [26] concluded that the oligodendroglia cells contribute to the formation of macrophages, although this is denied by Rio-Hortega, Penfield and others. According to Cramer and Alpers,[26] in experimental secondary degeneration of the spinal cord of rabbits, the oligodendroglia cells are the first cells to function as myeloclasts, and they later serve as both myeloclasts and myeloblasts in conjunction with the microglia cells.

EXPERIMENTAL TECHNIC

The rabbit was selected as the experimental animal, principally because of the ease of silver impregnation of the microglia and other interstitial cells of its nervous parenchyma. The animals were laboratory-bred males, free from disease and weighing from 4¼ to 5 pounds (2 to 2.25 Kg.).

They were anesthetized by ether, and a hole was bored with a hand drill through the right parietal bone 3 cm. to the right of the superior longitudinal venous sinus in order to avoid hemorrhage, visual disturbances and motor paralysis.

A puncture from 1 to 1.2 cm. in depth was made in the right parietal lobe with a sterile cold lumbar puncture needle in which the stylet was inserted. The injury served two useful purposes: (1) facilitation of the passage of colored semicolloidal and colloidal solutions into the nervous parenchyma by breaking the continuity of the hemato-encephalic barrier and by opening the smaller blood vessels and capillaries, thus establishing direct, physical contact of the surface of the interstitial cells with the dyes; (2) stimulation of an interstitial cellular reaction by the damaged brain tissue allowed to remain in situ. The operation was well supported. Not a single rabbit showed signs of infection either of the meninges or of the brain proper, and in not a single instance did paralysis follow.

A. Trypan Blue.—The dye in a concentration of 2 per cent was suspended in sterile triple-distilled water. A maximum concentration of 2 per cent was used in order to stain the wound tract and the neighboring brain tissue more deeply, if possible, than is the case with the 1 per cent suspension that has usually been employed by others. To demonstrate this, cerebral wound tracts were produced in a trial

22. Bratianu, S., and Guerriero, C.: Arch. d'anat. micr. **26**:337, 1930.
23. Verne, J.: Compt. rend. Assoc. d. anat., 1930.
24. Pruijs, W. M.: Ztschr. f. d. ges. Neurol. u. Psychiat. **108**:298, 1927.
25. Ferraro, A., and Davidoff, L. M.: Arch. Path. **6**:1030, 1928.
26. Cramer, F., and Alpers, B. J.: Arch. Path. **13**:23, 1932.

series of four rabbits which were then given 10 cc. of the suspension intravenously daily for seven days, while four rabbits with similar wounds received the same amount of dye over the same period but in a 1 per cent concentration. Sections from the brains and livers of both sets of animals counterstained with aluminum carmine and examined under a Zeiss comparison microscope revealed qualitatively a definitely larger number of stored dye particles in the cerebral macrophages and the reticulo-endothelial cells of the liver in the rabbits given the more concentrated suspension. At the same time, the toxicity of the dye used was observed; except for an almost negligible loss of weight, these heavy doses were not followed by toxic symptoms or signs.

Immediately before use, the solution was filtered to remove any aggregates capable of causing death by embolism and warmed to 37 C.

The animals in which trypan blue was used were separated into three groups according to the route of injection: (1) intravenous, (2) intra-arterial and (3) intraventricular.

Intravenous Injection: Ten rabbits received 10 cc. of a 2 per cent solution of the dye daily immediately after operation and five or six hours before death. Those surviving for two months received a total quantity of 600 cc., an amount certainly sufficient to produce at least a partial blockade of the so-called reticulo-endothelial system. Such a blockade would permit more dye than usual to reach the nerve cells capable of storing it. The animals were killed with chloroform after twelve, twenty-four, thirty-six, forty-eight and seventy-two hours and five, ten, twenty-four, forty and sixty days, respectively. The entire brain was removed immediately after death.

The puncture stab in the brain removed after twenty-four hours appeared as a slightly depressed, dark blue necrotic area, 2 mm. in diameter. The wound was frequently adherent to the dura and hemorrhagic at the margins and showed a moderate blue color in the necrotic center surrounded by a wider light sky-blue zone from which the color faded imperceptibly into the normal tissue. The dye was fixed principally at the site of the injured and dead tissue, and in contrast with the macroscopic appearance observed in the brains into which india ink and colloidal iron hydroxide were injected, it was highly diffused. Examination of the surface of the twenty-four hour brain with a Zeiss 20 × compensating ocular lens showed a zone of visible coloration extending 8 mm. from the central wound tract. Depending on the period of survival, the brain showed a progressively increasing intensity of blue staining in the central necrotic and hemorrhagic area, and the zone of reaction showed an increased width extending up to 13 mm. from the outer margin of the tract.

Intra-Arterial Injection: In order to bring a maximum quantity of dye to the injured brain before its deposit in other organs, intra-arterial injections were made in four rabbits. Immediately after traumatic injury of the parietal area of the brain, the carotid artery in the neck was exposed, and 10 cc. of a 2 per cent solution of trypan blue was introduced slowly into one of the smaller branches of the artery, which was then tied off. This procedure was repeated every other day, different branches of the same carotid artery being used. A rabbit was killed with chloroform every other day up to eight days after operation. The fourth rabbit, allowed to survive eight days, received therefore a total quantity of 40 cc.

Although unquestionably superior to injections into an auricular vein, injections into the carotid artery could not be carried out more often chiefly because of hemorrhage. Examination of the brains of the animals that had received intra-arterial injections showed a decidedly deeper intensity of staining than was present in

the brains of the rabbits given intravenous injections, but the distribution of the dye was essentially the same in both sets of animals.

Intraventricular Injection: Six rabbits without previous cerebral injury were given injections into the ventricles outside of the hemato-encephalic barrier so that an abundant amount of dye could be made accessible to the interstitial cells. After exposure of the dura, a syringe to which was attached a 2 mm. gage needle was gently passed through the gray and the white matter, and as soon as the needle appeared to be free in the ventricle, 2 cc. of a 2 per cent solution was slowly introduced. This was repeated every third day. The animals survived without any ill effects and were killed with chloroform from three to eighteen days after the initial injection. The brain tissue damaged by the passage of the needle was carefully removed because the dye penetrating from the ventricle into the gray and white matter had been taken up by degenerated or dead nerve cells, with the consequent production of artificial phagocytosis. Inspection of the brains revealed deep blue staining of the subependymal nerve tissue for from 1 to 1.5 cm. from the ependymal lining, with gradual but only moderate fading of color near the leptomeninges.

The rabbits given intravenous injections presented at autopsy an intense, deep blue staining of the skin, eyes, ears, liver, spleen and kidneys. The dura mater and the choroid plexus were deep blue.

B. India Ink.—Higgins' waterproof black drawing ink containing particulate carbon in colloidal suspension was selected as the source of the carbon particles for the phagocytic test. The ink was diluted with an equal volume of sterile triple-distilled water and immediately before use was warmed to body temperature.

Traumatic injury of the parietal lobe was produced as previously described in ten rabbits, which were then given intravenous injections of 10 cc. of the diluted ink daily for the first four days and then every other day until the end of eight weeks. The animals were killed after the same intervals and by the same technic as the rabbits into which trypan blue was injected. The stab wounds were from dark brown to almost black and surrounded by a zone of reaction from 2 to 4 mm. in width which was from light to moderate brown with sharp fading into the normal nerve tissue. So far as gross inspection permitted, it was evident that the ink possessed extremely slight, if any, power of diffusion.

C. Colloidal Ferric Hydroxide.—A colloidal suspension of ferric hydroxide was prepared as follows: Ferric chloride was purified by adding 95 per cent alcohol, drop by drop, until a precipitate was formed, and the solution was brought to a boil. The precipitate was filtered and dried. The presence of chlorine was tested for by the addition of 2 cc. of silver nitrate to the original filtered solution; a cloudy appearance indicated the presence of the chlorine ion.

To a freshly prepared half-saturated solution of purified ferric chloride (chemically pure) a 2 per cent normal solution of ammonium carbonate (chemically pure) was added in drops and with stirring until the precipitate formed just ceased to be dissolved. The solution was filtered if necessary and then dialyzed in a parchment tube against distilled water until only a trace of chlorine was detected. Gelatin was used as a protective colloid in an amount equal to about 0.073 per cent by weight. The solution was sterilized at 15 pounds' (6.75 Kg.) pressure for fifteen minutes in a steam autoclave. After sterilization, it was determined that the suspension contained 0.01147 Gm. of iron per cubic centimeter of liquid. The final solution was reddish brown.

A ferric hydroxide solution was also prepared as follows: Twenty cubic centimeters of a 2 per cent solution of ferric chloride (chemically pure) was gradually

added to 200 cc. of boiling water, and reddish-brown ferric hydroxide was produced by hydrolysis.

By repeated trial it was determined that the final preparation by either method was chemically inert and completely nontoxic for rabbits and that it was a complete suspension of submicronic particles. The serum of a rabbit in a dilution of 1:20 did not destroy its colloidal state in vitro, and therefore it was not surprising that it possessed the virtue of not producing minute emboli in the lung, as is so often the case with colloidal iron.

Before use, the liquid was allowed to stand for one hour to permit the suspended particles of iron to settle, and the supernatant clear fluid was carefully decanted. The concentrated suspension, each cubic centimeter of which contained 0.4588 Gm. of iron, was warmed to body temperature. Ten rabbits were given 20 cc. intravenously daily for two months after cerebral injury. They were then killed after twelve, twenty-four, thirty-six, forty-eight and seventy-two hours and five, ten, twenty-four, forty and sixty days.

It was clear from the gross examination of the brain that ferric hydroxide in colloidal suspension was only slightly, if at all, diffusible. The necrotic and hemorrhagic central core of the lesion appeared deep brown, and the zone of reaction, extending for from 3 to 4 mm., light to moderate brown.

D. Blood Pigment.—The behavior of the interstitial cells toward blood pigment was investigated by the production of a traumatic cerebral hemorrhage, with consequent formation of hematogenous pigment. Ten rabbits were employed for this purpose. They were killed with chloroform forty-eight and seventy-two hours and five, ten, fifteen, twenty, thirty, forty, sixty and ninety days after operation.

E. Bacteria.—The ingestion of bacteria by cells is a true phagocytic process. A strain of small Staphylococcus aureus isolated from a carbuncle, a strain of Streptococcus haemolyticus (strain 165) from infected tissue of a rabbit and a strain of Corynebacterium ulcerans isolated originally by Dr. Ruth Gilbert of the New York State Department of Health from a patient with ulcerative laryngitis were used. The last-named organism was selected because of its short length and because its morphologic characteristics precluded possible confusion with silver granules. All of the organisms were grown aerobically in dextrose brain broth and had a density in barium sulphate of from 1.5 to 2. In twenty rabbits, the cerebrum was exposed, and after injury of the leptomeninges 2 or 3 drops of the culture were allowed to fall from a glass capillary pipet over the injured leptomeninges. With the use of this procedure instead of direct injection of the bacterial culture into the nerve tissue, the micro-organisms were not forced into phagocytes, and the technical error of a false phagocytosis was avoided.

The animals treated with C. ulcerans were discarded because of the failure of the micro-organisms to multiply in loco. However, the injections of Staph. aureus and Str. haemolyticus produced infection in all of the animals, seven in each group. These animals were killed from two weeks to three months after operation, so that both acute and chronic lesions were studied and the time factor was eliminated. The streptococcic infections showed a spreading type of inflammation, with rare minute abscesses in the brain, while the staphylococcic infections were characterized by an occasional epidural abscess and by single or multiple abscesses in the brain walled off by a zone of glial and granulation tissue and associated with suppurative meningitis.

F. Fats and Lipoids.—The study of the reaction of the interstitial cells to neutral fats and lipoids presented two difficulties: (1) the inability to distinguish with certainty endogenous fat resulting from cytoplasmic degeneration from phago-

cytosed fat, and (2) the rapid breakdown and disappearance of stained neutral fat or lipoid emulsions. Thus, after the intraperitoneal injection into two rabbits of 10 cc. of a sterile solution of neutral fats of magnesium stained a deep orange color with scarlet red, the fat disappeared within two hours, as observed in frozen sections of the liver impregnated lightly according to the Hortega technic for macrophages.

In order to overcome these difficulties and to have as wide a variety of phagocytic test substances as possible, efforts were made by several chemists to prepare a colloidal particulate suspension of a neutral fat or lipoid which would satisfy all of the following requirements: (1) complete chemical inertia toward all of the reagents employed in the histologic technic to be described later; (2) staining by fat or lipoid stains, and (3) complete suspension of submicronic fat or lipoid particles. Unfortunately, such a preparation could not be developed, and therefore no study was made along these lines.

HISTOLOGIC TECHNIC

Immediately after the death of the animal, in order to prevent autolytic changes, especially in the oligodendrocytes, which are highly susceptible, Cajal's fixing solution, freshly prepared, was injected into the carotid artery toward the brain in order to secure the best possible cell preservation. A rectangular block of brain tissue with the wound in the center was then removed and immersed in Cajal's fixative. Many blocks taken at random from both cerebral hemispheres were also cut in order to rule out spontaneous encephalitis or other pathologic conditions. The blocks were frozen on the Sartorius freezing microtome and sectioned in the transverse axis of the wound at a thickness of from 10 to 15 mm.

Reduction of the black, silver-impregnated cell images was carried out to reveal simultaneously the complete cell and the phagocytosed test substances, thus eliminating a prime difficulty accounting for the differences in the results reported in the literature. The term "reduction" is used in its photographic sense, that is, the oxidation of some silver from the image by means of a reducing solution, with the production of a less intense or weaker image.[27]

The following criteria for reducing solutions for use in tissues were established and were completely satisfactory: (1) absence of oxidation of colloidal solutions; (2) uniformity of reduction in proportion to the intensity of the cell image without loss of cell structure; (3) formation of a permanent cell image composed of very fine and crowded lightened silver particles, and (4) ease of control of the degree of reduction.

After many trials of various silver reducers, ferric ammonium sulphate was found to meet completely all of these requirements, except in the case of blood pigments, which it oxidized, and it was adopted as the silver reducer for trypan blue, india ink, colloidal ferric hydroxide and bacteria. The original formula of Krauss[28] was modified by doubling the concentration of ferric ammonium sulphate, and the solution was prepared as follows:

Ferric ammonium sulphate (chemically pure)	4 Gm.
Sulphuric acid (concentrated)	1 cc.
Water to make	100 cc.

27. Elementary Photographic Chemistry, Rochester, N. Y., Eastman Kodak Company, 1924, p. 38.

28. Krauss, H.: Ztschr. f. wissensch. Phot. **18**:192, 1919.

Ferric ammonium sulphate acts as a proportional reducer, and photographically its reaction, according to Crabtree and Muehler,[29] is as follows:

$$2\ Ag + Fe_2(SO_4)_3(NH_4)_2SO_4 = Ag_2SO_4 + FeSO_4 + FeSO_4(NH_4)_2SO_4$$

Silver + Ferric Ammonium Sulphate = Silver Sulphate + Ferrous Sulphate + Ferrous Ammonium Sulphate

After immersion for twelve hours at room temperature in this solution, no oxidizing action was exercised on many trial frozen sections of mouse liver deeply stained with trypan blue, india ink, etc., and impregnated according to the Hortega technic for macrophages. Examination of these sections under the Zeiss comparison microscope, in contrast with those not reduced by ferric ammonium sulphate, revealed no loss of particles in the so-called reticulo-endothelial cells. Similar preparations of a kidney from a guinea-pig into which a lethal dose of Bacillus anthracis had been injected subcutaneously showed relatively slight reduction of the black-appearing bacilli as contrasted with the more marked reduction of the parenchymatous cells.

The reduction of each section was carried out at room temperature and carefully controlled under the microscope because of the frequent variation in intensity of silver impregnation in various fields of the same section.

The most suitable reducer for blood pigments was found to be potassium dichromate, which is photographically subtractive in action and attacks the photographic silver image, transforming it into silver carbonate and silver sulphates. It does not oxidize the blood pigments. The solution was prepared according to the formula of Crabtree and Muehler, as follows:

Potassium dichromate	0.1 Gm.
Sulphuric acid (concentrated)	0.1 cc.
Water to make	100 cc.

For the simultaneous demonstration of microglia cells and trypan blue, india ink, colloidal ferric hydroxide and bacteria, Hortega's technic as described by Penfield[30] was used with a few minor variations. A "strong" silver carbonate solution (molar) was substituted for the "weak" solution, as it yielded more constantly satisfactory results than the latter. After impregnation in the "strong" solution and subsequent reduction in a dilute solution of formaldehyde, U. S. P. (1:100), followed by thorough washing in triple-distilled water, the silver image was reduced with ferric ammonium sulphate for from a few seconds to two minutes, until all the microglia cells appeared from light brown to brownish gray. Toning with gold chloride was omitted, but the cell images were fixed in hypotonic solution and then thoroughly washed in four successive changes of triple-distilled water to wash out completely the residual silver extracted from the cells. The sections were then dehydrated in graded alcohol and cleared in either oil of origanum or a mixture of 95 per cent alcohol and carbol xylene, followed by two changes in xylene, and finally mounted in euparol.[30a] The sections impregnated with bacteria were controlled with the Gram-Weigert stain.

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29. Crabtree, J. I., and Muehler, L. E.: J. Soc. Motion Picture Engin. **17:** 1001, 1931.

30. Penfield, W., in McClung, C. E.: Handbook of Microscopical Technique, New York, Paul B. Hoeber, Inc., 1929, p. 380.

30a. A mixture of camsal, sandarac, eucalyptol and paraldehyde, used as a mounting medium instead of balsam.

For the simultaneous demonstration of microglia cells and blood pigment, impregnation for microglia cells was practiced as usual by very rapid reduction with potassium dichromate for from five to fifteen seconds, followed by thorough washing in triple-distilled water. Fresh 2 per cent potassium ferrocyanide and 1 per cent hydrochloric acid solutions were warmed to 37 C., and in a few instances to 56 C. The sections were immersed in each solution for five minutes, and the process was completed as usual except for mounting in Gurr's medium in order to preserve indefinitely the reaction to prussian blue. The Cajal fixative used was tested for iron and found to be free from it. The accuracy of the reaction was checked by staining at the same time sections of tissue known to be free from iron.

To demonstrate simultaneously oligodendroglia cells and trypan blue, india ink, colloidal ferric hydroxide, bacteria and blood pigments, the technic for oligodendroglia cells described by Penfield[31] was used, and only slight reduction with ferric ammonium sulphate or with potassium dichromate was found necessary to lighten the cells.

To demonstrate simultaneously astrocytes and trypan blue, india ink, colloidal ferric hydroxide, bacteria and blood pigments, Hortega's regular technic for astrocytes was employed, with ferric ammonium sulphate as a reducer, except that potassium dichromate was used for blood pigments.

In all of the preparations mentioned the general background varied from light yellow to light gray. The interstitial cells appeared from light brownish gray to light gray, and their processes, perinuclear cytoplasm and nuclei were clearly outlined and readily visible. The contrast between the cells and the colored particulate matter and bacteria was sharp.

The bacteria were relatively less reduced by the ferric ammonium sulphate than the cells, appearing from dark brownish black to black in contrast to the light brown to gray color of the cells. Unless involuted, their structure was identical with that shown in the Gram-Weigert preparations, and their recognition offered no difficulty.

TERMINOLOGY

The phagocytic cells of the brain have masqueraded under many names. Nissl introduced the term "*Gitterzellen*," now in wide use to indicate the lattice-like structure of the protoplasm after extraction of the fat. His term is objectionable because it indicates only one of many morphologic aspects assumed by these cells, their morphology being determined primarily by the nature of their biologic activity. Merzbacher's designation, "*Abraümzellen*," is more suggestive, calling to mind the removal of tissue débris and foreign bodies. Undoubtedly the name given by Metchnikoff, "macrophages," is the most suitable because of its connotation of the biologic property of the cells, the power of phagocytosis; this name is wisely chosen, moreover, because it does not imply a fixed ancestry. Therefore, the term "macrophages" will be used in this study.

For the classic neuroglia cells, the classification of Andriezen, grouping these cells into protoplasmic and fibrous astrocytes, will be adopted. I shall adhere also to Hortega's descriptive terms, "microglia" and "oligodendroglia."

31. Penfield,[30] p. 378.

MICROSCOPIC OBSERVATIONS AND INTERPRETATIONS

In control sections of the brains no microscopic evidence of any spontaneous pathologic lesions, such as perivascular mononuclear cell infiltration or focal necroses, was observed. The diffusion of trypan blue was most marked at the margins of the wound and faded gradually so that only scattered dye clumps were present in the normal-appearing nerve tissue. Some of the capillaries and small veins contained many crowded particles and clumps of trypan blue in their lumens. The colloidal ferric hydroxide and india ink preparations showed only a very slight degree of diffusion. The india ink was commonly present as solid irregular masses about the puncture tract and occasionally within the capillaries and small veins, and also, but rarely, at a distance away from the wound as scattered particles and clumps within the veins or the tissues. The ferric hydroxide never showed the clumping and massing manifested by the india ink, and most of the particles were concentrated in the zone of reaction and in the central core.

The sections impregnated with staphylococci revealed intense multiplication of the organisms, which were scattered over a wide area and were present in especially large numbers within the reactive zone. In contrast, the sections impregnated with streptococci showed fewer micro-organisms.

All of the sections were examined with the oil immersion lens. The criteria adopted for injury or death of the cells were those of Lewis and McCoy:[32] (1) loss of color of vital dye granules, (2) diffuse staining of the cytoplasm and nucleus and (3) the presence of particles of vital dye in the nucleus.

The close relation of form and function requires a somewhat detailed description of the structural changes in the interstitial cells reacting to the experimentally produced lesions.

Microglia.—Microscopically there was early and sharp mobilization of the microglial cells surviving injury in both the gray and the white matter outside of the limits of necrosis or hemorrhage. It embraced a more or less broad surface, depending on the type of lesion, but was wider and more intense around the experimental abscesses. The microglial reaction was presumably aroused in response to the chemotaxis exercised on the cells by the necrotic and degenerated products set free by the injury or death of the constituents of the neural parenchyma and by the presence of fixed vital dyes, blood pigment and bacteria. The microglia cells were the dominant cells in the acute lesions, rather than the oligodendroglia cells, as described by Cramer and Alpers. In the three day preparations changes of an evolutional rather than of a destructive character could be readily traced from the normal quiescent microglia cell, whether monopolar, bipolar or multipolar, to the fully developed

32. Lewis, W. H., and McCoy, C. C.: Bull. Johns Hopkins Hosp. **33**:284, 1922.

macrophage. The microglial reaction was brought about characteristically by mitotic division.

The initial changes appeared to consist of slight retraction and enlargement of the delicate lateral spines and of generalized early swelling of the entire cytoplasm of the cells. At this stage the nuclei retained

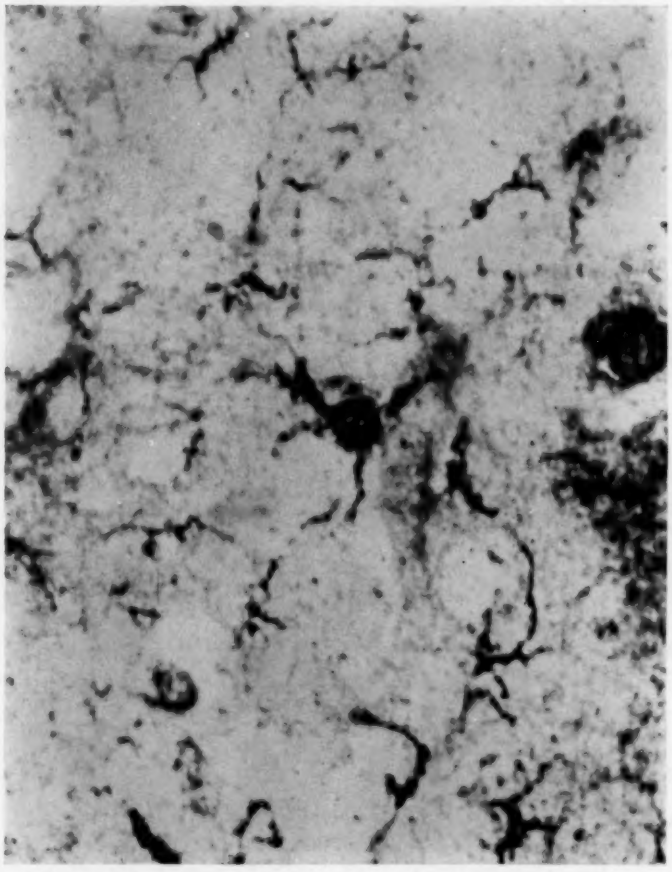

Fig. 1.—A hypertrophied microglia cell (center) containing crowded or scattered trypan blue particles in its thickened, retracted cytoplasmic processes (intracarotid injections of trypan blue; Hortega's silver carbonate technic for microglia cells; reduction with ferric ammonium sulphate; filter H 45 [Eastman]; Wratten "M" plate; magnification, × 1,100).

more or less of their characteristic form, and the cytoplasm was composed of crowded, fine, argentophilic granules.

As the center of the lesion was approached, the cell bodies continued to enlarge and became rounded, with progressive retraction, thickening and loss; first the secondary lateral spines were thus affected and then

the main branches. The nuclei appeared more or less black and more varied in shape. Bipolar rod-shaped cells with long, straight or curved nuclei and elongated, thickened processes streaming out from each end of the perinuclear cytoplasm were not infrequently seen.

The structural changes continued in the next phase, culminating in the formation of macrophages. The outstanding microscopic feature of the cells was their remarkably varied polymorphism, which may have been conditioned by the initial form of the cells; this could not be

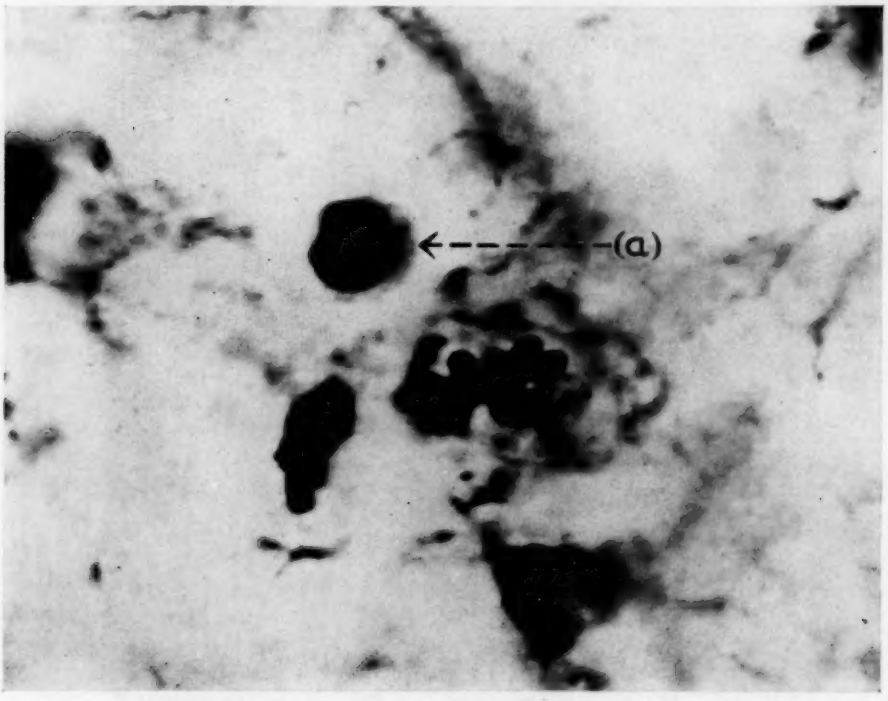

Fig. 2.—Early acute swelling of an oligodendroglia cell (*a*) lying close to masses and particles of india ink injected intravenously, showing absence of carbon particles in the cytoplasm of the cell (Hortega's silver carbonate technic for oligodendroglia cells; slight reduction with ferric ammonium sulphate; magnification, × 1,800).

verified with certainty, however, by observation of fixed sections. The nuclei were impregnated either darkly or lightly. There were further enlargement and rounding of the cell bodies. Some of the transitional cells with one or two short, rounded or pointed, tuberose stumps resembling pseudopodia were practically indistinguishable from ordinary macrophages fixed in the act of movement. Cells of this type persisted in the subacute and chronic stages but were especially rich in the reactive

zones of the acute experimental inflammations. Their cytoplasm was composed of argentophilic granules of varied form and dimension and presented a more or less well developed spongy, reticulated structure. A relatively small number of the cells had undergone partial to complete cytolysis. Their nuclei were inseparable from the cytoplasm, and they

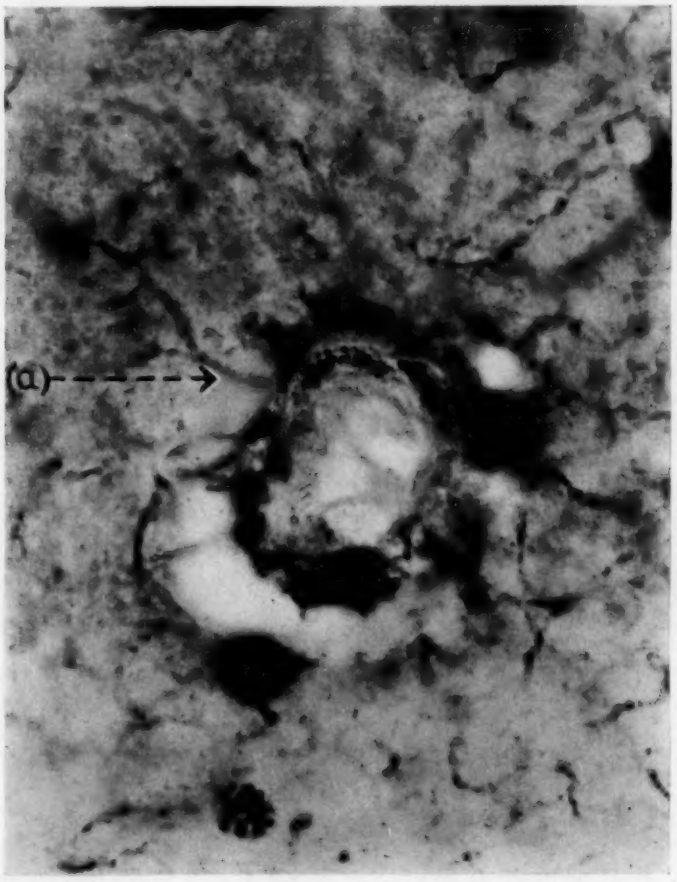

Fig. 3.—A cerebral capillary with india ink particles in the cytoplasm of the endothelial cells, showing absence of carbon particles in the perivascular foot of a fibrous astrocyte attached to the wall of the capillary (*a*) (Hortega's silver technic for astrocytes; reduction with ferric ammonium sulphate; magnification, × 1,350).

also showed the usual microscopic changes of injury or death in the vitally stained preparations.

Most of the microglia cells were widely distributed, but some had mobilized as satellites about degenerated or necrosed ganglion cells, nerve fibers and astrocytes. Some lay close to capillaries and small

blood vessels but never applied their cytoplasmic processes to the walls of the former or to the pia-glial membrane surrounding the latter.

A minority of the transitional microglia cells stored a variable number of discrete or crowded particles of trypan blue, colloidal ferric hydroxide, india ink and blood pigment and had phagocytosed as well both staphylococci and streptococci.

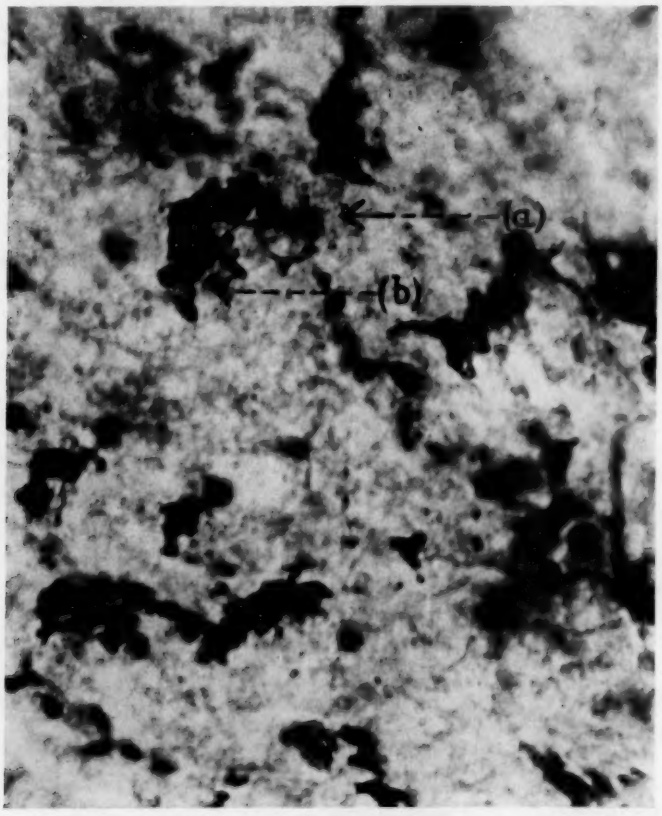

Fig. 4.—Hypertrophied, transitional microglia cells within the reactive zone about an experimentally induced Staph. aureus abscess (Hortega's silver technic for microglia cells; no reduction; magnification, × 1,100). This figure illustrates the difficulty of distinguishing bacteria (*a*) from unreduced microglia cells (*b*) lying about them.

A few microglia cells with colored particles of varied form and dimensions were noted. These were interpreted as representing the technical error of the phagocytosis of previously stained extracellular material pointed out by Bratianu and Guerriero. Only those cells with uniformly sized and shaped particles of vital dyes in their cytoplasm were accepted as examples of true phagocytosis. Undoubtedly, the

storage of dye particles leads to the development of cytoplasmic changes such as those observed in the transitional cell forms.

It must be emphasized that the majority of transitional cell forms did not store even readily accessible blood pigment granules or vital dyes. In this respect, they behaved differently from specific endothelial cells, which regardless of their situation take up colloidal dye with great avidity. On the other hand, they resemble in a restricted sense normal lymphocytes which never ingest vital dyes until, according to Maximow, they are transformed into monocytes or macrophages. It seems that

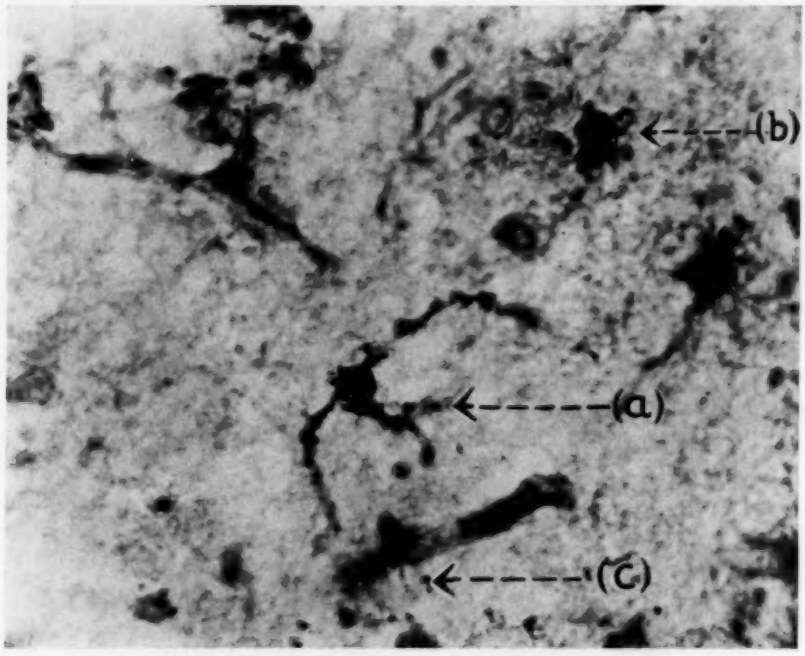

Fig. 5.—Phagocytosis of swollen micrococci, Staph. aureus (*a*), by a hypertrophied microglia cell. Note the neutrophile with phagocytosed micrococci (*b*) and scattered micrococci (*c*). (Hortega's silver technic for microglia cells; reduction with ferric ammonium sulphate; magnification, × 1,200.)

the microglia cells must be activated by a sufficiently strong stimulus and pass through certain structural changes before they can carry out the function of phagocytosis.

Most of the dye-storing cells were observed among the moderately to far advanced transitional cells and in the animals which were given the largest amounts of vital dye. The nearer the cell approached in structure the macrophage, the more dye it ingested. The persistence of the function of the microglia cells after storage of vital dyes, whatever the mechanism may be, indicates that the structures taking up the

dyes are not vitally concerned in the life of the cell. Only the cells saturated with dye eventually died.

No storage of vital dyes, blood pigment or bacteria was observed in normal or dividing cells. The absence of dye in cells undergoing mitotic division is undoubtedly bound up with the problem of phagocytosis, the exact mechanism of which is still obscure. It is also evident that there

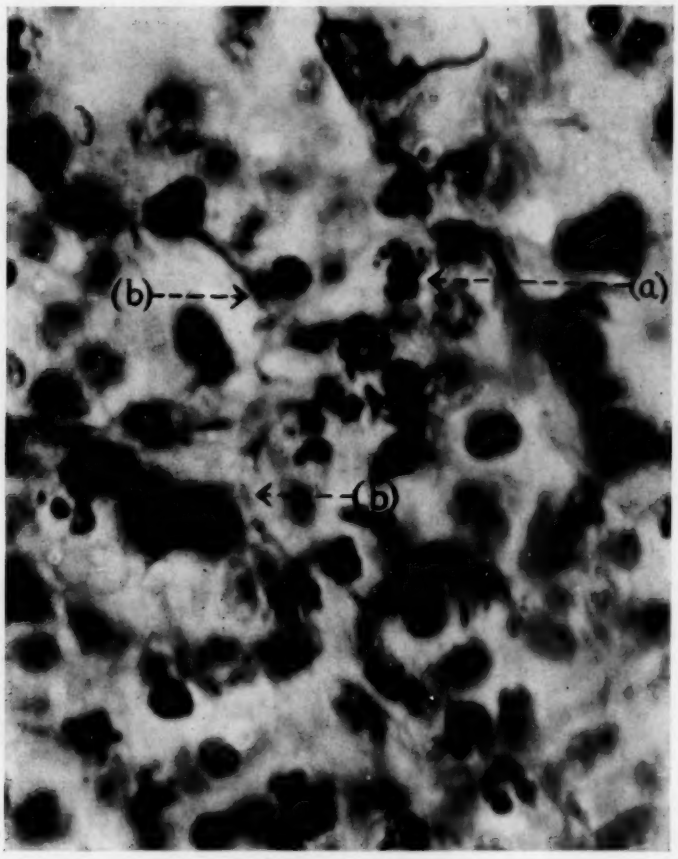

Fig. 6.—Proliferated fibrous astrocytes within an experimentally induced Str. haemolyticus inflammation. Note phagocytosis of micrococci by neutrophils (*a*) and their absence in the neuroglial processes of astrocytes (*b*). (Hortega's silver technic for astrocytes; reduction with ferric ammonium sulphate; magnification, × 1,350.)

exists some relation between the maturity of the microglia cells and their power of phagocytosis for colloidal dyes, bacteria, etc. As for the absence of dye in the normal resting cell, there are two possible explanations: (1) that because of the almost negligible visible quantity of dye

in their neighborhood the cells do not store dye in a sufficient amount to be observed microscopically, because the particles of a vital dye must aggregate in clumps of a certain size before they are microscopically visible and (2) that the microglia cells do not possess the power of locomotion and therefore ingestion will not take place unless the cell and foreign dye particles or bacteria come into physical contact with each other.

The storage of vital dye is not an exclusive property either of macrophages or of cells of mesenchymal origin. In vivo, there are several exceptions to the rule that all dye-storing cells are mesenchymal in origin. For example, it is recognized that the epithelial cells of the choroid plexus are of ectodermal origin, and yet these cells store dye in large quantities without furnishing phagocytes. Therefore, although the transitional microglia cells in the rabbit's brain reveal a definite capacity to take up vital dye, a mesenchymal origin cannot be ascribed to them on this basis alone. In a personal communication, Maximow stated: "All macrophages, irrespective of their situation, are exclusively mesenchymal in origin. We can affirm this not because they have the properties of taking up the vital dye—any cell can, after all, ingest dye particles under suitable conditions—but because this is known from innumerable embryological and pathological conditions." Therefore, the decisive demonstration of vital dyes in transitional microglia cells, coupled with the basic investigations of Hortega, Penfield and others indicating their origin from embryonal meningeal polyblasts and their transformation into macrophages under pathologic conditions during adult life, points to their mesenchymal origin.

The phagocytosis of blood pigment by some of the transitional microglial cells was observed as early as the fifth day after the experimental production of hemorrhage, increasing proportionally with the increase in the age of the hemorrhage.

As in the case of vital dyes and blood pigment, the resting and dividing microglia cells never phagocytose bacteria. This function is performed in the first three or four days of the experimental infection primarily by the polymorphonuclear leukocytes, and only later by a minority of the transitional microglia cells. Thus, the capacity of transitional microglia cells to phagocytose both bacteria and vital dyes runs pari passu.

Neuroglia.—The changes in the astrocytes vary in degree, depending on the nature, severity and duration of the lesion and on the type of astrocyte involved. The most intense regressive and hyperplastic changes were observed about the experimental abscesses. There is a mixed reactive zone composed principally of macroglia and to a lesser extent of granulation tissue about the wound tracts, abscesses and hemorrhage. The earliest reactive changes in the astrocytes were observed in the

forty-eight hour preparations. The astrocytes do not appear to enter into a syncytium but seem to react as separate cellular units. They show slightly increased irregularity, nuclear pallor and fine granular and pale irregular swelling of their cytoplasmic and fibrous processes, associated not infrequently with neutral fat inclusions. The latter are evidently of intracellular origin, since no extracellular fat was observed in the neighborhood of the cells. In the acute stages, the astrocytes situated directly about the center of the lesions frequently undergo partial to complete clasmatodendrosis, as described by Cajal. The cell bodies are markedly swollen, the nuclei show karyorrhexis or pyknosis and the processes are disintegrated or broken up into fragments, clustered about the cellular remains. The great majority of them evidently disappeared, as they were very rare in the older lesions, especially in the traumatic lesions under discussion. In fact, there was a conspicuous absence of astrocytes immediately about the wound tracts and the center of the abscesses in the three and five day preparations.

Astrocytes corresponding to the *gemästete* cells of Nissl were frequent in the margins of the chronic wounds and abscesses. They presented a voluminous, finely granular cytoplasm from which passed forth thick, irregular processes and large, darkly impregnated, eccentrically placed nuclei. The more chronic lesions also showed swollen cytoplasmic bodies and irregular swelling and varicosities of their dendrites in the process of dendrophagia by satellite cells.

Before the third day there was no tendency to increase on the part of the astrocytes, but thereafter they multiplied by amitotic or direct division. The reactive zone of hyperplastic astrocytes was progressively broadened. The damaged nerve tissue appeared to act as a stimulus to the macroglial reaction, for with its gradual disappearance the reacting astrocytes were reduced proportionally in number.

After division, the daughter cells generally took more or less the form of the mother cell, but they differed from the normal astrocyte by possessing more pale, irregular and enlarged nuclei and more rounded cell bodies. Binucleate forms were common. Not infrequently, especially about the abscesses, transition forms, apparently between the protoplasmic and the fibrous astrocytes, were noted. Two weeks after the production of the lesion, the astrocytes were present in conspicuous numbers and threw out fibrous processes to form a young glial feltwork laid down radially about the wound and abscesses. At the end of twenty-four days, the macroglial reaction had reached its height, the glial feltwork showing increased thickening and containing relatively sparse nuclei.

The membrana limitans gliae beneath the pia mater, capillaries and small veins frequently showed regressive changes and contained within

its meshwork occasional wandering macrophages, astrocytes and cocci, single or in clumps, but never any microscopically visible particles or aggregates of colloidal dyes.

Except for occasional diffuse or granular vital staining of dead or injured astrocytes, the latter, whether present in an acute or chronic traumatic or infective lesion, fibrous or protoplasmic, mature or immature, hypertrophic or hyperplastic, preserved or degenerated, under no circumstances stored vital dyes or phagocytosed bacteria or blood pigments.

Oligodendroglia.—The initial reaction of the oligodendrocytes in the first seventy-two hours after injury consisted of the characteristic changes described by Penfield and Cone as acute swelling. This reaction was transitory, being rarely encountered in the later stages. It was, as a rule, more regular and intense in the gray matter about the lesion than in the white matter. The cells underwent hypertrophy, with a voluminous increase in cytoplasm and pyknosis of the nuclei, followed by hydropic degeneration of the cytoplasm. A certain number of the cells disintegrated and disappeared, while others reverted to their original state. They were frequently massed about blood vessels, and their short expansions passed occasionally transversely or parallel to the blood vessel wall but never into the pia-glia membrane. Other cells were mobilized as satellites about degenerated ganglion cells.

As early as the third day after injury slight hyperplasia was observed, which increased somewhat one week later but subsided thereafter.

The oligodendrocytes did not appear to give rise to macrophages and never exhibited any phagocytic activity toward colored colloidal ions, blood pigments or bacteria.

Blood Vessels.—The local activity of the capillary endothelial cells in the immediate vicinity of the wound tract was slight in contrast to that observed around the abscesses. They rarely showed signs of increase, and mitotic figures were extremely uncommon. Many endothelial cells, especially those situated at the margins of the wound, were swollen as a result of cytoplasmic degeneration or of immaturity. These sometimes contained blood pigment granules, or more rarely particles of trypan blue or colloidal ferric hydroxide, when injured, but no living cells stored either of these two colloidal solutions frequently present in the lumens of the vessels. In the sections impregnated with india ink the common endothelial cells constantly stored carbon particles, but no storage was noted in common fibroblasts. According to Lang, this phenomenon is not a true active phagocytosis but is due to a peculiar condition of the surface tension of the cells. No transformation of any of the endothelial cells into macrophages with desquamation into the lumens of the vessels was observed. Failure of the endothelial cells

to take up colloidal ions or bacteria places them outside the class of phagocytic specific endothelial cells.

Sprouting young capillaries about the wound tract were observed only occasionally and were never sheathed by adventitia and rarely invested by dye-containing phagocytes. Polymorphonuclear leukocytes were present for seventy-two hours, disappearing almost completely thereafter. Careful search within the vessel lumens for cells having the morphologic characteristics of monocytes or macrophages was entirely fruitless. The absence of such cells suggests that in all likelihood no phagocytes reach the brain from other organs.

Fusiform, rounded and enlarged cells containing dye, blood pigment and bacteria were constantly observed within the adventitia of small, medium-sized and large vessels. Comparison with sections taken from rabbits which were neither traumatized nor inoculated with dye showed that these cells could not be distinguished from other cells situated in the adventitial mesenchymal network. Further comparison with sections from inoculated but nontraumatized rabbits showed that in the traumatized brain there was a constant and definite increase of dye-containing cells, which was due to proliferation in loco rather than to any cells accidentally wandering into the network. These cells correspond to the adventitial macrophages described by Marchand and Renaut in fixed and stained sections. They represent a barrier to the diffusion of dye into the nerve tissue, supplementing the protective function of the meningochoroidal barrier.

The perivascular spaces which accompany the perforating vessels were dilated and frequently distended with dye-storing or nondye-storing macrophages. Their lining mesothelial cells also stored dye in large quantities. By desquamation and passage into the perineuronal spaces about the ganglion cells, these cells may possibly represent the so-called neuronophagic glial cells, but this could not be demonstrated with certainty in sections cut in one plane.

Macrophages.—The structure of the macrophages was varied, depending on the nature of the ingested substances. They were most abundant in the zone directly about the necrotic or hemorrhagic centers. They ranged from 9 to 15 mm. in diameter, the younger forms being, as a rule, smaller than the older ones. When free and fully developed they were large and rounded and possessed, as a rule, a small and eccentric nucleus. The nucleus was bounded by a prominent nuclear membrane against which lay most of the chromatin, scanty and usually concentrated into one or more bodies. The cytoplasm was abundant; it was honeycombed or reticulated, and in the spaces between the delicate cytoplasmic strands were interspersed lipoids, blood pigments, nuclear fragments or dye particles. Sections from the staphylococcic abscesses and diffuse streptococcic inflammations showed frequently macrophages

with phagocytosed, broken-down polymorphonuclear leukocytes and bacteria. Infrequently, the cytoplasm of the macrophages was sharply separated into a pale, vacuolated endoplasm, and an ectoplasm, now broad, now narrow, more deeply stained and either vacuolated or reticulated in appearance. Mitotic figures were present, especially in the later stages, but they were never numerous. Amitosis was occasionally seen. Care was taken not to confuse cells undergoing amitosis with deceptive binucleate forms containing a phagocytosed nucleus. A certain number of macrophages were evidently short-lived, undergoing either injury or death, as indicated by diffuse vital staining of the cells or by the entrance of the dye into their nuclei.

The earliest macrophages rarely stored vital dyes, a fact which can be hardly explained on the assumption of specialization of function in such a lowly differentiated cell. This failure seems to be a question of the amount of dye accessible to the cells rather than of any elective affinity, because with the increase in the amount of dye administered, more and more macrophages accumulated dye particles in increasing quantities. Thus in the ten day preparations, at least one-third of all the macrophages contained dye particles in their cytoplasm. The dye granules varied considerably in size, some reaching a diameter equal to that of the cell nucleus, apparently representing the staining of previously ingested necrosed material. No dye crystals were observed within any macrophages.

CONCLUSIONS

1. Silver reduction demonstrated the phagocytosis of colored colloidal particles, blood pigments and bacteria by a minority of the transitional microglia cells in experimental lesions in the rabbit's brain but not in normal resting and dividing microglia cells.

2. The storage of vital dyes by transitional microglia cells is an additional fact pointing to their mesenchymal origin.

3. No phagocytosed vital dye particles, blood pigment granules or bacteria were observed in silver-reduced neuroglia and oligodendroglia cells.

4. There is a distinct relationship between the phagocytic capacity of the microglia cells and their maturity.

5. The failure of the endothelial cells of the cerebral vessels of the rabbit to store vital dyes, blood pigment, bacteria, etc., places them outside the class of specific phagocytic endothelial cells.

6. The actively phagocytic adventitial cells of Marchand supplement the protective function exercised by the hemato-encephalic barrier.

General Review

PATHOLOGY OF UNDULANT FEVER

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While the entire literature of undulant fever has been fairly prolific of recent years and not inconsiderable for half a century, the strictly pathologic portion is limited. There are related aspects, though, that particularly concern the pathologist or other laboratorian. The study has involved him not only in the discernment of postmortem evidences but even more in the recognition of the disease during life, in preventive measures and in the baffling problem of treatment.

By far fewer data appear on the morbid anatomy of the disease than on the bacteriology and serology. Pathologists leave the impression that little is to be said thereon. Much of what is recorded has been only incidental to clinical observation. I cite disproportionately here from such scant notation—having a balanced pathologic picture in view—and allow major consideration to the morbid changes, but it is with the express understanding that this phase of the subject does not find a correspondingly substantial footing in the literature.

Few diseases depend more on the laboratory for a clear definition. Except when the disease is known to prevail through the community, a diagnosis can hardly be established without laboratory test. Encountering the more pronounced form of undulant fever in localities where it is generally prevalent, Marston was able to differentiate it symptomatically from typhoid fever and other acute ailments. He was the first to recognize it as a definite disease. Students of the one epidemic known in the United States (Lake) commented on the extreme difficulty of making a diagnosis from clinical symptoms alone early in the course of an outbreak or in the absence of one. Others (Gilbert and Coleman) have shown how often the disease fails to be recognized, its manifestations being too mild to reach the physician or too indistinct to be diagnosed.

Though it is widely disseminated in this country, the condition was long missed altogether. Craig (1906) first recognized the situation, proving a case to have been contracted in this country and suggesting

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the likelihood of many, though they were confused clinically with malaria, typhoid fever, tuberculosis, pneumonia, septicemia, relapsing fever, Hodgkin's disease and rheumatism. This confusion has in no way cleared up since. Recent literature only enlarges the list of confusing conditions: typhus fever and tularemia (Mason, 1931), kala-azar (Loewy), influenza (Clouston), surgical conditions such as appendicitis and cholecystitis (Simpson, 1932), pyonephrosis (Demaree) and an indisposition too indefinite for any clinical impression except myocarditis (Clark). Members of the medical profession have diagnosed cases through laboratory procedure.

More than one condition comes into consideration as undulant fever. These various manifestations are caused by distinct varieties of the infective organism and are not identical clinically. The best studied, and until recent years the only one known, is that of caprine origin, which caused devastations at Mediterranean posts compelling the attention of British military surgeons late in the nineteenth century. Earlier literature designates it by any of a dozen or more different names, usually as "Malta" or "Mediterranean fever." Most of the names seemed less and less appropriate as knowledge of the condition broadened, and the name "undulant fever" occurred to Hughes (1896) as a more descriptive and less ambiguous term. Preference eventually settled on this designation, and international endorsement was accorded it in medical gatherings (Blanchard, Bassett-Smith, 1914). Forms of the disease more recently defined, and related etiologically to contagious abortion in the cow and hog, are sometimes referred to in contradistinction as "abortus fever," but more generally they are also designated as "undulant fever."

BACTERIOLOGY

The septicemic character stands out in the pathologic picture of the condition. On microscopic section Bruce (1887) found coccoid bacterial forms in the spleen of a patient who died late in 1886, and the following year he cultivated the organism. Later he succeeded in cultivating it from the blood of patients during life. Tissues throughout the body yield the culture: blood from the heart, the spleen, liver, gallbladder, kidneys, suprarenal glands, pancreas, thyroid gland and many of the lymph nodes (Bassett-Smith, 1922). The organism may remain cultivable for long periods in the blood or other tissue of an infected person. Burnet (1922) found that it was cultivable from bone marrow when not from the blood. A positive culture has been reported from the spleen after eighteen months (Bassett-Smith, 1922) and one from an ovarian cyst after six years (Wainwright, 1929*a*). Various observers have found the organism in the joints, the tonsils, the ovaries, the oviduct, the epididymus and practically all the parenchymatous organs

(Carpenter and Boak, 1931). Strains vary greatly, however, in the activity with which they invade these tissues.

The micro-organism was described in some detail by Eyre (1907). Though so persistently spherical as to support a definition of coccus (Eyre, 1926), its capacity for rod formation also establishes it in practically all the current classifications as a bacillus. That of Winslow and his collaborators included it in the genus Bacterium with a note that data not yet on hand might constitute it a new genus. Meyer and Shaw, and Feusier and Meyer applied to it the name Brucella, which ever since has met with general enthusiasm among workers with the organism. The classification of Lehmann and Neumann left it in the genus Bacterium but recognized a subgenus Brucella, as it did a subgenus Pasteurella. Bergey and his collaborators first classified it in Castellani and Chalmers' genus Alcaligenes, attributing its initial omission from the genus to a doubt as to its bacillary form. This generic terminology likewise found proponents among the writers on undulant fever, but in its last revision Bergey's (1933) classification recognizes instead the genus Brucella.

Differentiation of Organisms.—Literature on bacterial characteristics concerns principally the differentiation between types. Undulant fever was first attributed to the type infective primarily for goats. Evans (1918*a*) pointed out a close antigenic relationship between it and the bacillus of infectious abortion in cattle. Agglutination tests that readily differentiated the latter from the bronchisepticus organism failed to distinguish it from that of undulant fever except by a difference in titer. Further study brought forth many antigenic types. By absorption of agglutinin Evans (1925) distinguished in her series an abortus, a melitensis A, a smaller melitensis B, a para-melitensis, a para-abortus and three other types of a single strain each. Feusier and Meyer described four serologic groups, with abortus strains falling in group I, melitensis strains in I, II or III, and para-melitensis strains in group IV. Serologic grouping was not a simple one.

Type differentiation was undertaken in a number of laboratories, but far from clearing the situation it disclosed more and more divergence and multiplicity of types. It was suggested that the para-melitensis-abortus groups be considered mutant or rough types of the smooth melitensis-abortus (Ross, 1927*a*). Provision for smooth and rough variants leaves the classification even more cumbersome, but the failure to distinguish between them has been held accountable for some of the difficulties (Wilson, 1931). Serologic grouping into so many varieties seemed to Bassett-Smith (1925) premature and confusing, and he regarded the indication of pathogenicity as a more useful guide. Others expressed themselves similarly (Duncan). Not only did the patho-

genicity test avoid what seemed a superfluity of bovine and caprine types, but it also differentiated an important type obtained from swine.

Distinction by pathogenicity rests primarily on the natural infectivity for goats, cattle or swine. Pathogenic activity in laboratory animals helps a little to classify organisms isolated in human undulant fever. Theobald Smith's (1926) descriptions show how strains of the different origins may produce a more or less distinctive pathologic effect in guinea-pigs. One group tends to greater pathogenic activity than another, and strains less highly virulent cause lesser degrees of endothelial proliferation and other morbid change presently to be detailed. The method's weakness in differentiative ability is shown by the variability of result from diverse sources of experimentation (Strong). The most practicable evidence it gives is that porcine strains, indistinguishable serologically from the bovine, produce pathologic effects more closely approximating those produced by the caprine strains. A serologic in conjunction with a pathologic test thus provides some means for separating all the strains into the three groups. Rainsford subgroups his strains serologically and by the production of hydrogen sulphide into melitensis and abortus, and then the latter by inoculation of animals into bovine and porcine strains. He gets better results with hamsters than with the more generally utilized guinea-pigs.

Biochemical behavior offers additional points of distinction between the organism's three main varieties. The differentiation by the hydrogen sulphide test, just referred to, agrees uniformly with that by absorption of agglutinin. This substance is liberated by both of the abortus forms but not by the melitensis, when grown on Stafseth's liver infusion medium, and is indicated by lead acetate (Huddleson and Abell, 1927). The liver medium is often adopted for isolation of the organism. Huddleson, Halsey and Torrey (1927) use it with gentian violet to inhibit the growth of any gram-positive flora present. They cultivate at 37 C. aerobically for fifteen hours, then continue some cultures for ten days aerobically and others for seventy-two hours in an atmosphere replaced by from 5 to 10 per cent carbon dioxide.

The change in cultivation atmosphere facilitates the growth of the bovine type of organism. When first describing his abortus bacillus, Bang suggested a procedure for the reduction of oxygen, though not its elimination by pyrogallol (Bang). Huddleson showed that the advantage of sealed tube growth lay not in the low oxygen tension but rather in the increased concentration of carbon dioxide. Caprine strains, on the other hand, though facultative anaerobes (Eyre, 1907), are much retarded if deprived of a free supply of oxygen and do not benefit by additional carbon dioxide in the atmosphere. The porcine strain, like the caprine, grows in the air from the first generation, and on passage through animals may be reisolated from the tissue strictly aerobically

(Good and Smith). With fresh strains this same differentiation is made from the degree of utilization of dextrose: not over 2 per cent by the bovine as compared to from 5 to 20 per cent by the other strains (McAlpine and Slanetz).

Huddleson (1931) also described a differential test depending on the varying bacteriostatic action of such dyes as thionine and either methyl violet or basic fuchsin. Thionine in the employed concentration inhibits the bovine, the other two dyes the porcine, and none of them the caprine, strains. In a large illustrative series tested, 325 strains fell into the first, 172 into the second, and 133 into the third, of these respective groups. Unlike the absorption or other tests already described, this reaction by itself differentiates all three types. Its dependability is variously evaluated by others. According to one comparison of a classification of 19 strains on this basis with that by absorption of agglutinin, there was agreement in 9 and disagreement in 10 strains (Francis, 1931).

Recent classifiers of strains have preferred to employ several of or all these various bases of differentiation rather than to choose between them. Serologic, pathogenic or cultural distinction is not of itself sufficiently clear to make it possible to disregard the others. Blake and Oard, for instance, employ and advise absorption of agglutinin, inoculation of guinea-pigs, the carbon dioxide requirement and utilization of dextrose for the routine differentiation of all the human strains.

Classification is carried at least to caprine, bovine or porcine designation. These varieties are generally recognized. Others may assume importance locally, for instance the one prevalent in Rhodesia according to Bevan (1925) and Duncan. Duncan defined this strain as presumably bovine but differing from the bovine as heretofore described in that its cultivation atmosphere need not have additional carbon dioxide. Evans (1925) regards all these varieties as of a single species, Brucella melitensis. Others continue to separate as Brucella abortus the organisms derived from contagious abortion of cows or swine. Eyre (1926) could not justify from his strains a relationship even this close between the two. Bruce's organism, unlike Bang's, remained persistently coccus-like, and cultural differences seemed distinct.

Transmission of Infection.—For many years following Bruce's description of the organism the infection continued as an ill-comprehended scourge disseminated no one knew how. Its devastations were felt continually by British army posts of the Mediterranean and by neighboring civil populations. Eventually the admiralty and war office, cooperating with the civil government of Malta, established the Mediterranean Fever Commission to investigate the cause of the disease and consider preventive measures. Studies conducted from 1904 to 1906 established several points. The infection was septicemic in goats and

sometimes localized in the udder. The common means of contraction by man was through ingestion of milk from infected animals. Less common was subcutaneous inoculation through abrasions incidental to handling (Eyre, McNaught, Kennedy and Zammit). How closely the prevalence in the military and civil population of Malta was related to the consumption of goat milk is brought out by the Commission (McCulloch, Weir and Clayton) and further elaborated on by Eyre (1912).

The likelihood of transmission through goats excited immediate attention elsewhere, and brought contributory observations pro and con. Sergent, Gillot and Lemaire, for instance, determined by agglutinative reaction of the milk and by cultural study the proportion of infected goats in Algiers. Some other potential sources of infection were hard to set aside, and direct contact was still suggested to Ross (1906) by the high prevalence in hospitals, houses or barracks where the disease localized. He observed, too, that sailors picked up the disease ashore and that they did not drink milk.

Undulant fever of the type under investigation at Malta must have prevailed then and ever since in the southwestern part of the United States. Gentry and Ferenbaugh found it endemic through the older goat-raising sections of Texas and noted that a disease of like symptomatology had been known among the people for at least twenty-five years. Thirty-four per cent of the goats tested gave positive agglutination reactions. Yount and Looney associated the occurrence also with the goat industry in Arizona, and the same situation extended to other neighboring states (Kampmeier). Herds of goats thereabouts and in Mexico proved on survey to be extensively infected (Holt and Reynolds). In this endemic area, as in Malta, the control of the disease has been effected primarily and principally through supervision of the supply of goat milk (Tappau).

The undulant fever of caprine origin was encountered and recognized over a large part of the globe before any other form was suspected. In 1914 Bassett-Smith stated that wherever the disease is found, in Italy, India, South Africa and America, goats are practically always present and distribute it, but that other ruminants may carry it. At about that time certain analogies with contagious abortion in cows began to appear. The abortus organism described by Bang had been recognized in this country as elsewhere (MacNeal and Kerr), and Evans (1918*b*) noted its close resemblance to the organism of undulant fever. She found it present, though not continuously in large numbers, in milk taken from the udders of cows that had aborted, indicating a possibility of human exposure. Other suggestive data accumulated, and Keefer reported a case of undulant fever with evidence of such bovine origin. Subsequent evidence clearly established this etiologic relationship. In

one experiment, pregnant heifers were inoculated with organisms isolated from human cases, and they aborted and yielded the organism in culture from the fetus, placenta and colostrum (Carpenter, 1927).

Histories of patients with undulant fever soon proved to accord with a possible infection from this source. In one series of 38 cases, 17 patients had been in contact with cows that had aborted and 12 drank raw milk (Weigmann). Again, of 82 persons whose occupation brought them into close contact with infected cattle, the serums of 22 gave positive agglutination or complement-fixation reactions or both (Kristensen, Helms and Martensson). Six gave positive agglutination reactions at 1 : 100 or over, and 1 had a symptomatic case of undulant fever, while control persons all gave negative reactions.

While the abortus organism thus showed a definitely invasive property, this activity was of less degree than that of the melitensis organism. A lesser invasiveness for monkeys on experimental feeding was shown by Fleischner, Vecki, Shaw and Meyer. Burnet (1928) showed the same for man on injection. Morales-Otero's (1929, 1933) feeding experiments in man indicated a less infective character of strains from cow's milk, the strictly bovine in particular. Comparisons drawn by Kampmeier showed that in man such infections ran a milder course clinically than those transmitted by goats.

An extremely low rate of attacks contrasts with the frequency of abortus organisms reaching the milk supply. Carpenter and Boak (1928) found that the cream of over 6 per cent of an arbitrary series of cows' milks contained the organism infective for guinea-pigs. McAlpine and Mickle presented presumptive evidence of wide exposure to infection in Connecticut, and yet contraction of the disease by man was limited in that locality. With 90 per cent of dairy herds infected and only 60 per cent of the milk pasteurized, only 0.6 per cent of 10,157 random serums received for a Wassermann test agglutinated the abortus bacillus in dilutions up to 1 : 100.

In view of the wide dissemination in market milks, it must be this relative avirulence of the abortus organism that spares much of the world from ravages such as those experienced in Malta. It is interesting to contrast the situation regarding undulant fever about the Mediterranean and other foci of caprine infection with that in countries in which cattle constitute the sole source of infection. There is reason to presume that infected cow's milk has been the only common vector in Great Britain (Dalrymple-Champneys, 1931). The Board of Agriculture and Fisheries long ago confirmed the widespread existence of epizootic abortion among the cattle in England, Wales and Scotland (McFadyean and Stockman, 1909), and the milk or serum of cows in London has agglutinated the organism in high dilution (Kennedy, 1914). The infection of goats does not appear, though Broadbent reported as an exception an atypical case supposedly contracted from a goat.

Great Britain has little clinical undulant fever but apparently a more considerable prevalence of subclinical infection—reasonably attributable to heavy exposure from contact or from the milk of aborting cattle—with low susceptibility (Wade). Cruickshank and Barbour found that a hospital population altogether without evident undulant fever gave positive agglutination reactions in a little less than 0.5 per cent of instances, and they associated these instances with exposure to infected cattle. The same situation was reported for Scotland by Marr and by A. Thompson for Ireland: Infectious abortion of cattle is rampant, but undulant fever in man is exceedingly rare.

It was not long before Brucella abortus of the swine type was found among the organisms accountable for undulant fever. The type of abortus organism that causes the larger portion of infections in swine had been described (Cotton) as an aberrant type, infective for both cattle and swine, and producing in guinea-pigs a lesion different from that caused by strains affecting cattle alone. Smith (1929) thought that it may have developed from the bovine type through the feeding of hogs with dairy by-products. He found (1926) that strains of this variety produced lesions in guinea-pigs much more like those produced by some human strains than did the bovine variety. Evans (1925) suggested the possibility of porcine infection. The studies made in Iowa particularly showed its wide extent. An instance occurred with 3 infections of the bovine type but 1 strongly suggestive of the porcine type (Awe and Palmer). Further instances accumulated, and the probable proportion of cases of porcine infections increased (Bierring). Kern mentioned infection with undulant fever resulting directly from hog carcasses, but it also developed that many infections from cow's milk were caused by porcine organisms infecting cattle (Blumer). A study of 11 cases of undulant fever in Georgia (Atwood and Hasseltine) indicated their causation by porcine strains transmitted through the milk supply.

The porcine strains show greater virulence for man than the true bovine strains. By feeding them to man, Morales-Otero (1929) produced typical undulant fever with a positive blood culture and in 1 case an agglutination reaction, but he failed with bovine strains. Huddleson (1929) similarly obtained greater pathogenicity for monkeys by feeding. The extent to which contagious abortion gives rise to clinical undulant fever seems to depend on the preponderance of organisms of the porcine type. The infrequency in northern Europe and, as rule, in this country may be attributed to a relative rarity of exposure to porcine strains, to whose attack human tissue is more susceptible (Hasseltine, 1929).

The widespread presence of Bang's bacillus had suggested appropriate treatment of the milk supply even before milk-borne undulant fever was known. Melvin considered contamination with abortus organisms another link in the chain of facts establishing proper pasteurization

of all market milk as a measure essentially necessary for protection of the public health. Without professing to know what effect this organism might have on human beings, he would not assume that there was no effect. Recognition of the transmission of undulant fever through milk amply sustained the contention. State health departments have included infectious abortion with tuberculosis as diseases to be eliminated from dairy herds (King). Experiments conducted under the Bureau of Animal Industry (Cotton, 1924) showed that vaccination is futile and suggested more likely control through separation of herds to weed out the infection. Until this can be accomplished, for a number of years anyway, Hasseltine (1930) suggested pasteurization as the sheet anchor in the prevention of milk-borne undulant fever.

Virulent porcine as well as bovine strains in milk are destroyed by pasteurization, though their thermal death point is twenty as compared with fifteen minutes at 140 F. (Carpenter and Boak, 1933). Pasteurization had been early suggested in connection with infected goats' milk, including that used in ice-cream or native cheeses (Eyre, McNaught, Kennedy and Zammit). The organism survives the handling procedures incidental to the manufacturing of these products, and there is a possibility of contracting undulant fever from ice-cream frozen a month or more (R. Thompson).

It soon developed that the disease, even that caused by the strictly bovine strain, is commonly transmitted otherwise than by cow's milk. The transmission appears to be principally by milk in some localities and, according to some, throughout the country (Simpson, 1930). Starr and Maxcy noted that about 60 per cent of the cases in Virginia are so transmitted, compared with 40 per cent of cases due to contact with animals. The extensive incidence in Iowa was not distributed like a milk-borne infection (Hardy, 1928). Milk would probably have brought the largest percentage to the city, whereas 145 of 209 cases were rural. The much greater rate of attack in males than in females and to some extent the vocational and age incidence suggested rather the contact with cattle and hogs (Bierring). Raw meat sometimes appeared to be a disseminating agent (Moorehead).

Contraction of the infection is rare except by transmission in some manner from one of the three kinds of animals. There is no evidence of transmission from man to man (Simpson, 1930). In spite of this a proper disposal of the urine and feces has been urged (Carpenter and Boak, 1933). The organism readily reaches the urine and the feces, apparently through the bile (Bassett-Smith, 1922). Elimination is principally by these excretions.

The danger of accidental infection in the laboratory is by no means negligible and has been said to occur even more readily than with glanders or plague bacilli (Widal, Léon-Kindberg and Cotoni). While such

cases are rarely reported, laboratory workers have been known to pick up the infection from suspensions or cultures. Huddleson (1926) mentioned an infection of a graduate student working with the organism, though he was more suspicious of raw cow's milk which had been consumed. Before the Mediterranean Fever Commission had demonstrated the common avenue of transmission, accidental infection had already been observed repeatedly. Bassett-Smith (1904) in his description of the undulant fever situation among naval forces at Haslar expressed the belief that the usual path of transmission was by dust and wind, but he pointed out how readily the organism in laboratory cultures caused attacks if taken in by mouth or accidental inoculation. Prior to that he (1902) had mentioned a number of instances of accidental infection.

Incidence of the Disease.—Before proceeding with the pathologic identification of cases of undulant fever, one might consider just where and among what groups of persons these cases are likely to be encountered. Distribution charts changed radically, of course, with recognition of the relatively mild forms associated with contagious abortion. They now show the occurrence of the disease practically throughout the civilized world (Dalrymple-Champneys, 1933). When the only known areas of infection showed the goat-borne fever, the condition was passed over with other tropical diseases by most pathologists. The known incidence extended broadly between the forty-fifth parallels north and south through all the continents except Australia, but large areas within this zone seemed unaffected. Apparent freedom from the disease was often due to inadequate diagnostic skill, but some countries with such advanced medical facilities as Great Britain reported no cases (Bassett-Smith, 1922). In the United States practically all the diagnosed cases were imported prior to the reports cited from Texas. Some occurred among persons from abroad, especially soldiers and sailors from the Philippines or other tropical stations (Curry; Craig, 1903; Mason, 1903).

Craig (1906) first reported a case as having been contracted in the United States, that of a nurse in Washington, D. C. Even at that time he thought that the disease was much more widespread than is usually supposed and suggested serodiagnosis of undetermined fevers in all regions. Gentry and Ferenbaugh (1911) described a considerable prevalence of undulant fever in the Rio Grande valley and subsequently a report came of the one epidemic recorded for this country, in Phoenix, Ariz. (Lake). This form of the disease, contracted from goats and due to the melitensis type of organism, has remained limited to that section of the country—Texas, Arizona, Utah and Nevada. The disease so widely described elsewhere is that contracted from cattle or swine and due to the abortus types of organism (Wainwright, 1929*a*).

Undulant fever due to the abortus organism was supposed to be infrequent when it was first described (Keefer), but during the few

years following, case after case appeared. Unlike the cases of caprine origin, these were generally distributed through the country. A review of the first 20 showed 1 case in Washington, D. C., 2 in Maryland, 1 in South Dakota, 1 in Connecticut, 7 in New York, 1 in California, 3 in Utah, 1 in Virginia and 3 in Michigan (Evans, 1927). The prevalence became most extensive in Iowa (Hardy, 1928). A survey soon showed a greater or less occurrence in three fourths of all the states (Blumer), with reports still coming in from others (Carey and Newsom). It was realized that undulant fever probably exists in all and is likely to prove rather prevalent wherever carefully searched for (Moorehead).

The season exerts some rather inconstant influence on the prevalence. Like other milk-borne infections, undulant fever from the first has been encountered most in the summer (Hughes, 1897). The abortus like the melitensis form has this seasonal tendency. Official tabulations in the United States for 1929 and 1930 showed the larger proportion of cases reported in the summer and autumn, reaching peaks in July and September, respectively, but the duration of the cases prior to report was unknown (Hasseltine, 1931). Scattered observation of others lacks uniformity and fails to attach significance to any seasonal rise noted.

The rural cases far outnumber the urban. The melitensis form presents only one exception, the outbreak in Phoenix (Lake). The clearest evidence in the abortus form comes from the numerous cases in Iowa, with a rate per hundred thousand of 11.4 in rural districts, 8.3 in towns of under 5,000 population, and 4.0 in larger cities (Hardy, 1929*c*). Reports from abroad, from Denmark for instance (Kristensen, 1928), also suggest a predominance in rural districts and insignificant seasonal changes.

Occupation has more to do with infection from goats than from cattle and swine. Of the 5 cases reported by Ferenbaugh, 4 were in goat herders and 1 in a goat ranchman, and except at Phoenix this occupational relationship is borne out by subsequent observation from that section. Similar influence might be expected with infections from cattle or swine in which milk is not the vector, since proximity to these animals depends on occupation, but it has not been found so distinct a factor (Wainwright, 1929*b*). In four selected localities during the prevalence of the disease in Iowa, the percentage distribution was as follows: among farmers and their wives, 31.6; employees in packing houses, butchers and veterinarians, 6.9; business and professional men, students and laborers, 39.4; housewives, 16.8; children and invalids, 3.9, and laboratory workers, 1.4 (Hardy, 1929*c*).

Evidence presumptive of subclinical infections, consisting in a positive agglutination reaction of the blood serum, is sometimes more suggestive of occupational influence. Of 49 veterinarians, 3 of whom had a history suggesting clinical undulant fever, 57 per cent showed agglu-

tinins in the blood and 26 per cent showed a reaction at 1 : 100 or above (Huddleson and Johnson, 1930). Again, complete agglutination was demonstrated in 33.4 per cent of 120 veterinarians, in 24 per cent of 220 employees in packing houses (13.6 per cent reacted at 1 : 80 or above) and in 16.5 per cent of 138 consumers of raw milk (3.6 per cent reacted at 1 : 80 or above) (Jordan).

The age of attack ranges from early childhood to old age, but most cases fall in the 20 to 44 year groups. About two thirds of the patients in the Iowa series were in these age groups (Hardy, 1929*c*). The infection is exceptional in infancy or early childhood, but cases are described; one occurred in a child aged 1 year on a cow's milk formula (Kohlbry), and 1 in a child of 7 months on breast milk (Hill and Monger). Certain authors in describing the disease in children (Anderson and Pohl) have noted the relatively mild character of these cases, the attack being hardly noticeable except for a persistent fever. They think that the disease may be more frequent in children than is commonly believed.

MORBID ANATOMY

The literature is not yet adequate for a clear conception of the morbid anatomy of undulant fever. Authors of textbooks on pathology make little attempt to cover the subject and have practically omitted it except in the most recent issues. Boyd devoted two pages thereto, but only a small part of this matter described pathologic lesions and it featured the toxic and other changes common in septicemias. He mentioned the rarity of postmortem studies in explanation.

The postmortem material is limited by a low fatality rate, less than 2 per cent according to Boyd. Occasional virulent outbreaks have been attended by a considerable number of fatalities. According to the report of one exceptional outbreak 160 of 630 inhabitants contracted the disease, and 40 died (Aubert, Cantaloube and Thibault). The early figures from Malta indicated a fatality rate of 2.3 per cent among 1,705 navy and 1,947 army men, or of 6.9 per cent of a total of 4,627, combining these cases with those in civil administration (Eyre, 1908). The greater proportion of cases of bovine origin are mild and rarely fatal (Leavell, Poston and Amoss). They may have a fatality rate approximating 2 per cent (Kristensen, 1928). With so few of these cases on record as yet, the total rate for undulant fever can only be surmised.

The bulk of the postmortem observations that have reached the literature are practically negative. They rarely establish a postmortem diagnosis, the simplest procedure for which is through culture of the spleen, liver, kidney and mesenteric gland (Topley and Wilson *a*). Morbid changes that would create a picture in any way distinctive have been encountered too rarely to suggest that they are uniformly produced by the disease. On the other hand, since most reports are recent, it is

conceivable that newer refinements of observation and technical procedure are developing a pathologic concept missed until now. The few observations of that nature on record may prove a nucleus for a more characteristic entity.

Earlier postmortem observations are best expressed in a treatise by Hughes (1897). A summarized report is made of 60 postmortem examinations of hospitalized soldiers at Malta; 15 of these were seen by the author. In the acute cases gross examination revealed an intense congestion, especially marked in the internal organs. The chronic cases showed a similar change, though less constant or pronounced, and also various effects of the long continued irritation of the tissues. The microscopic study added nothing of significance except that in the spleen a larger proportion than usual of lymphoid tissue was evident. A postmortem examination of later cases shows little more for the most part, when made as a routine and reported only incidentally as these were. One random report (Hardy, Jordan, Borts and Hardy) gives as the most striking feature a complete absence of any gross pathologic changes, and the only microscopic ones a chronic interstitial pancreatitis, chronic cholecystitis, fatty infiltration and passive congestion of the liver, and myocardial degeneration with fragmentation, not especially significant of undulant fever.

Other recent observations are reported because they attract special interest in the pathologic changes and are perhaps new to the literature. It is these that one scans most hopefully for any characterisitc change that may hitherto have escaped notice. One finds them scattered thinly through a volume of inconsequential observations. Unfortunately, they are not only exceptional but highly variable and conflicting. As Wohlwill said in reference to abortus disease in man, there are submitted at the present time quite striking dissimilarities of the pathologic anatomic conditions. Each observation must stand more or less by itself. Since the first report of any extraordinary occurrence bears various interpretation, significant evaluation of these observations cannot immediately be made.

A question arises not only as to the characteristic cellular reactions but also as to the extent to which the infection actually causes the pathologic changes encountered. The uncertainty subsides only as the picture recurs. One finds endocardial involvement first regarded as probably rheumatic (Hughes, 1897; Scott and Saphir), since the literature on undulant fever did not feature it, but later considered as localization of the undulant fever infection (De La Chapelle, 1929). Considerable pathologic involvement is associated with the disease by evidence too scant for conviction.

The solution must come as postmortem data accumulate in more considerable volume. Quantities of such matter must be filed away in the

records of pathologic laboratories, but in isolated notations of themselves too doubtfully significant for publication. I recall a case in the John Sealy Hospital at Galveston with clinical and selorogic aspects warranting report (Stone). Subsequently it disclosed complications with pathologic changes that support and possibly add something to the general picture I shall present, but of itself this feature established too little for an additional report. Findings of bronchopneumonia, pleurisy, arthritis, a rheumatic type of cardiac disease, congestive cardiac failure and acute cystitis were presented at various times. Paralysis agitans and other central nervous derangement, including a pronounced psychosis, also developed. Autopsy revealed gross and microscopic evidence of atheroma of the aorta, hypostatic pneumonia, acute splenitis, purulent cystitis and pyelitis and atrophy and fatty degeneration of the liver. Permission for examination of the brain was not granted. Such conditions are often associated with undulant fever but also with other diseases, and much of their significance lies in the relative frequency.

Without adequate data to pass on the import of pathologic observations, we must be content for the present with a survey of whatever morbid changes are found described. The resulting concept will not be quite true to the disease, perhaps far from that. One can only hope that it may serve pathologists as a basis for comparison in autopsies and encourage the ultimate evolution of a truer picture.

The most essential item in the general pathologic alteration is a proliferation of cells belonging to the reticulo-endothelial system. This has been elaborated on repeatedly of recent years, and earlier postmortem descriptions of different phraseology offer nothing inconsistent with it. In many cases the proliferation is described as not only pronounced but as sufficiently distinctive to help differentiate the disease from other conditions.

Nodular Reactions.—A more or less definite type of infectious granuloma is suggested, the most striking feature of which is a nodular lesion resembling the tubercle. From many quarters something of this sort is described, though not with the same regularity at autopsy as in infected animals. The respective descriptions of histologic structure lack uniformity, however, and leave doubt as to whether they all define the same pathologic reaction; that is, while similar nodules are mentioned by a number of authors, these lesions are not obviously of the same type.

In some instances the histologic picture resembles that of the tubercle. Confusion with concomitant tuberculosis has arisen, but in most cases this mixture of infection seems to be clearly ruled out. Wohlwill described this lesion most distinctly in a case he studied. He said that the nodules were somewhat smaller than millet seeds and of fairly uniform structure. The latter picture was completely overbalanced by

large epithelioid cells having clear, moderately coarse eosinophil, finely granular, or in any case not generally homogeneous, protoplasm and pale nuclei with scant chromatin. Their shape was rarely round, but as a rule oval, hooked, curved or otherwise irregular. Fairly regularly admixed with these were a number of eosinophil or rarely neutrophil granulocytes. In a few of the nodules were occasional giant cells, some resembling Langhans' cells and some having nuclei scattered irregularly. Fat was distributed over the epithelioid cell bodies in fine droplets, making the nodules conspicuous in sudan-stained preparations, but whether this had any importance Wohlwill could not yet say. There was no tendency to caseation.

Points of similarity occur in the histologic structure as described by others. The cellular aggregation is not always in defined nodules (Rössle), nor do defined nodules always consist of a similar cellular aggregation. Some lesions with a superficial resemblance to the tubercle are quite dissimilar in microscopic structure. Gregersen and Lund described nodules consisting of simple fibroblasts and lymphocytes scattered in the fibrous layer, without epithelioid cells. Wohlwill cited Löffler and von Albertini as having found in the pulp of a spleen some older and partly cicatrized nodules that contained plasma cells and were surrounded by fibrinous exudate. Rothenberg described a case of perisplenitis which showed translucent nodules of pinhead size, with hyaline change, scattered over the splenic surface.

While these nodular reactions have been defined most clearly in the spleen, they are also encountered in the lymph glands, bone marrow and other tissues. Hansmann and Schenken described meningeal nodules consisting of hyalinized connective tissue infiltrated with chronic inflammatory cells, large mononuclears surrounded by a collar of lymphocytes. In a patient with undulant fever and tuberculous infection Amoss (1931) found peritonitis simulating tuberculosis. There were white papules softer than tubercles and with a histologic resemblance to them, containing giant cells and lymphoid infiltration. Such a condition has points of similarity to the more marked reaction that sometimes follows a positive allergic cutaneous reaction for undulant fever. The induration, instead of disappearing after a few days, develops into a local granulomatous lesion with a grayish point that suggests underlying pus but on incision produces no pus or bacteria (Giordano).

This tuberculous structure appears much more uniformly and distinctly in infected animals. Gregersen and Lund interpreted findings in man by their approximation to the results of experimentation with animals. The patches they saw in animals showed a structure more like tuberculosis, with a predominance of epithelioid fatty granular cells, while corresponding human lesions showed simple fibroblasts.

In guinea-pigs the resemblance to a tuberculous reaction is so close that it has confused the interpretation of laboratory inoculation tests. Fleischner and Meyer (1917) suggested that earlier testing of milk supplies may have erred because the anatomic lesions in guinea-pigs infected with bovine abortion disease were mistaken for those of tuberculosis. Schroeder and Cotton found that lesions mistakable for tuberculosis are caused by some other organism present in milk, but one not readily identified from their description.

Histologic observations in guinea-pigs are well described by Theobald Smith (1926). In the spleen and lymph nodes a proliferation of endothelial type cells develops, resembling the cells focalized by tuberculosis but not undergoing the same retrogressive changes. They retain stains feebly and give the impression of rarefied areas. This proliferation was not excessive with strains originating from bovine abortion, to which the animal was only moderately susceptible. Polymorphonuclear leukocytes appeared rarely at the center of the focus, when of maximum size, and necrosis practically never. With human strains of greater virulence for guinea-pigs, the foci began similarly, but in two or three weeks they enlarged until they were grossly visible as yellow masses, 2 or 3 mm. in diameter, sharply outlined but not raised. Infiltration with polymorphonuclear leukocytes paralleled the enlargement of the endothelial focus, and a central necrosis sometimes developed. The entire gland was eventually converted into an enlarged firm mass, with coalesced foci. The inconstancy with which a like manifestation has been encountered in man may have some analogy with this contrasting degree of reaction of guinea-pigs to different strains. The tissues may be regarded as insusceptible to the tuberculous reaction in most subjects but are driven to it in the occasional least refractory instances, their reaction then comparing with the milder ones in guinea-pigs. This is only a conjecture, visualizing significance in observations as yet extraordinary. Experiments with inoculation of monkeys have led to the development of similar nodules. One 2 mm. nodule in the lung was described microscopically as a focus of small round cells, and a 6 mm. nodule as one of reticulo-endothelial cells and leukocytes, suppurating at the center (Huddleson and Hallman, 1929).

Necrosis is characteristically absent in the nodular areas in man and occurs more in other organs than in those showing this type of reaction. Conspicuous necrosis of hepatic cells marked the involved patches of that organ in Wohlwill's case, leaving little but an empty framework of connective tissue and persisting capillaries. In contrast with the splenic condition, epithelioid cells were seldom found here. Bassett-Smith (1922) noted a necrosis of the hepatic tissue yielding a positive culture without true pus.

The suppuration described in pronounced nodular lesions in guinea-pigs is likewise absent in man, but suppuration is by no means rare as a complication of undulant fever even in apparently pure infections. In one patient a subdiaphragmatic and hepatic abscess developed (Eyre and Fawcett). A large cavity extended into the liver with necrosis of the organ's substance, and an aspirated specimen yielded the bacillus of undulant fever in pure culture. Abscesses are also reported at other sites, for instance, in the anterior mediastinum (Hardy, Jordan, Borts and Hardy) and in the iliac fossa (Tilghman).

The polymorphonuclear defense is evidently not prominent. The blood picture almost uniformly reveals a decrease of polymorphonuclear and an increase of mononuclear cells. The two changes may result in the raising or lowering or in essentially no change of the total white cell count. Simpson and Fraizer found a slight leukopenia in three fourths of their cases and a normal count in the others. Amoss (1931) found that leukocytosis was the usual response, with 30, 40 or even 80 per cent lymphocytes. Diminution in the number of polymorphonuclears seemingly results from their destruction rather than from bone marrow inhibition, since the proportion of immature nonfilament type cells is increased (Gallagher).

An actual lymphocytosis occurs quite generally and irrespective of the type of organism producing the undulant fever. In the cases of caprine origin early described in Texas, Gentry and Ferenbaugh reported a differential leukocyte count of 45 per cent polymorphonuclears, 47.6 per cent small mononuclears, 4.4 per cent large mononuclears, 2.2 per cent transitionals and 0.8 per cent eosinophils. Similar mononucleosis appears in tabulations of the epidemic in Phoenix that developed subsequently (Watkins and Lake). When Keefer first attributed undulant fever to the abortus type of organism, he found on repeated counts that the lymphocytes rose to as high as 52 per cent and the large mononuclear-transitional group to 22 per cent. Of course there are exceptions. In one diagnosed case there was a leukocytosis of 16,000, of which the polymorphonculears constituted 71 per cent (Broadbent).

Spleen.—The splenic tissue exhibits greater pathologic changes than any other. It was in parts of the spleen that the tubercle-like formations were presented most distinctly. Wohlwill (1932) found them to be most clear and numerous in the malpighian corpuscles, and not in the splenic pulp. Gregersen and Lund described nodules in the pulp, and so did Löffler and von Albertini as cited by Wohlwill. Other microscopic changes have little evident significance. The occurrence of accumulations of certain cells is in accord with observations elsewhere. In keeping with the blood formula, a preponderance of large lymphocytes and large mononuclears are described in splenic smears and in section

their infiltration about the vessels (Archibald). Macrophages are reported in the sinuses, in which red blood cells and pigment and multinucleate giant cells are engulfed (Rothenberg).

The most obvious and general gross change in the spleen is an enlargement. The early cases described by Hughes (1897) were so characterized, and many others since have shown that condition. Muir's textbook of pathology hardly mentioned undulant fever except in connection with a splenic tumor. This author gave the average weight of the organ as a little over 1 pound (0.5 Kg.), with a tendency to progressive increase as the disease progresses. The degree of enlargement varies extremely. The weight is frequently normal, and sometimes, on the other hand, it reaches 1.58 Kg. (Bassett-Smith, 1922). Schottmüller described a patient with an extraordinary swelling, the anterior pole extending to the navel. One of the outstanding physical signs of the condition is a palpable spleen. Manson-Bahr and Willoughby and many others have emphasized it in describing their cases. In the tropics this has confused the splenic index of malaria (Hislop). Infection with the abortus as well as with the melitensis type of organism is characterized by this variable degree of enlargement. Hardy (1929*b*) found the spleen enlarged in 37 of 125 cases with infections from cattle and swine.

The enlargement results from lymphoid hyperplasia. In his early descriptions of the disease, Bruce (1889) noted that the malpighian bodies were enlarged owing to an increase in the number of round lymphoid cells. This has been generally confirmed since (Strong, 1931). One illustrative record shows somewhat prominent trabeculae and a moderate increase in the pulp (Strong and Musgrave), and many others give similar reports.

The earliest descriptions suggest septic softening (Bruce, 1889). Hughes (1897) described the tissue as appearing almost diffluent, even broken-down and rotten or like a large clot of venous blood. To subsequent pathologists this softening has not seemed so characteristic, and its occurrence has been attributed in part to a postmortem change. The organ has often been found quite firm, perhaps fibrous (Archibald, Tyndale and Viko). Bassett-Smith (1922) suggested an increasing tendency to firmness as the disease becomes chronic. The enormous spleen in Schottmüller's case, several months advanced, was quite solid. Löffler recorded that the diagnostic splenic tumor is larger and more solid than the spleen in typhoid fever.

Passive hyperemia of the spleen is common. Intense congestion on section, with sinuses enormously distended with blood, was observed by Bruce (1889) and subsequently by many others. Incidental observations include small hemorrhages (Bassett-Smith, 1922), organized

thrombi in the trabecular veins (Gregersen and Lund) and anemic infarctions (De La Chapelle). In Rothenberg's case the surface of the spleen showed an acute localized process taking the form of tubercle-like nodules. Perisplenitis is more often encountered in its later effects. In one case tough sheetlike and stringlike adhesions bound the spleen to the diaphragm and to the peritoneum externally (De La Chapelle).

Lymph Nodes.—Changes analogous to those in the spleen occur in the lymph nodes. There is likely to be hyperemia of the capsule (Eyre, 1908) and of the gland on cut section (Strong and Musgrave). Enlargement is not infrequent. Beginning with Bruce (1889) many authors have mentioned a swelling of certain lymph nodes, usually including the mesenteric. Occasionally this enlargement is general (Wainwright, 1929*b*). Palpable and often painful nodes, sometimes located in the neck, may occur early or late in the disease and have sometimes been regarded as diagnostically significant (Rodriguez). The enlargement results from reticulo-endothelial hyperplasia. Descriptions have disclosed this most distinctly along the course of the sinuses (Hardy, Jordan, Borts and Hardy); irregular compression of the sinuses has been known to result (Rössle).

The nodules reminiscent of tubercles have been found well defined in the lymph nodes. Wohlwill encountered them most numerously in the periaortic nodes, their character being like that of the lesions he described in the spleen. Rössle described a distribution of large cells through the lymphoid tissue, in an ill-defined aggregation near the margin but gathered into nodular accumulations deeper in the gland. He noted the resemblance to early stages of tuberculous infection. De La Chapelle found occasional minute white points suggesting miliary abscesses in swollen and edematous lymph nodes. Histologic changes of this character might in some cases contribute to the laboratory diagnosis. In Cruickshank and Cruickshank's case, therefore, a gland was excised, but only lymphatic hyperplasia was found.

As in the spleen, necrosis is exceptional. Katsch described to Wohlwill a reactionless, purulent infused necrosis in numerous groups of lymph nodes. Eyre (1908) mentioned the occasional presence of semi-fluid purulent content in mesenteric nodes. Necrosis and ulceration have occurred similarly in the follicles of the intestine. Bruce (1888) mentioned a few such instances in Peyer's patches, but he noted them only as exceptions to qualify the general observation that ulceration does not occur. The rarity of ulceration in Peyer's patches has always been recognized in the differentiation of undulant from typhoid fever. As a rule, follicles, like nodes, have shown no other change than a slight swelling and cellular hyperplasia (Strong and Musgrave).

Hughes (1897) found patches of intestinal hyperemia in nearly all the cases of his series. As a rule, the alimentary tract shows nothing except this. Ulceration occurs only rarely in the mucosa and then, as a rule, elsewhere than about the lymph follicles. Mention has been made of aphthous patches in the mouth (Müller), of peptic ulcer (Amoss, 1931) and of undermined ulcer in the ileum (Bruce, 1888). Intestinal irritability on roentgen examination has suggested ulceration of the large intestine (Griffin). This, like infection of the gallbladder which also occurs (Amoss, 1931), may help to explain the abdominal pain and tenderness occasionally prominent in the symptoms of undulant fever. Auerbach (1932) mentions a case with symptoms at times of gastritis or gastric ulcer and again of appendicitis or cholecystitis.

Liver.—The liver more than any other organ shows a tendency to necrosis. A degeneration about the central veins (De La Chapelle) with centrolobular necrosis (Hardy, Jordan, Borts and Hardy) has been described. Another case showed this process advancing farther until in patches only the empty framework of tissue remained (Wohlwill). In one case a large hepatic abscess was present (Eyre and Fawcett).

Hepatic tissue fails to show at all distinctly the cellular aggregations that sometimes characterize the spleen and a few other organs. In Wohlwill's case they were merely indicated in the affected patches of hepatic tissue. Epithelioid cells were seldom found and then had plenty of room, in contrast with the compressed aggregates elsewhere. Infiltrations of small round cells are frequently mentioned; often they are situated in the interlobular tissues (Bruce, 1889). Increase in connective tissue also occurs in the interlobular areas (Strong and Musgrave).

In many cases the liver is enlarged, though not as markedly as the spleen. In one case the organ was enlarged to 2.94 Kg. (Bassett-Smith, 1922). The enlarged, firm, nutmeg-like liver depicted in a random description (Tyndale and Viko) seems fairly typical. Passive hyperemia develops as in other organs. Hemorrhages occur; in one case they were minute and superficial just beneath the capsule (Strong and Musgrave). Cloudy swelling and fatty change are frequently noted.

Kidneys.—Changes in the kidney are pronounced only with complicating nephritis. This complication has been on record since Bruce's work (1889), and with renal insufficiency and uremia has sometimes been the cause of death (Baastrup, 1928). Hemorrhagic cases are described. In that of Strong and Musgrave there were hemorrhages throughout the viscera, and the kidneys were dark and extensively hemorrhagic. In another there were scattered extravasations through the cortex and about some of the glomeruli, with a beginning atrophy of the latter and infrequent hyalinization (De La Chapelle). In the latter case some yellowish specks suggestive of miliary abscesses and

an infiltration of small round cells about some of the Bowman's capsules were also mentioned. Except in instances of nephritis the kidneys show no significant changes. Not infrequently there is some enlargement, hyperemia or cloudy swelling.

Genital Tract.— Any involvement of the genital tract naturally attracts attention, since uterine inflammation is the chief manifestation of the infection in cattle and swine. When the organism of contagious abortion was found implicated also in human disease widespread speculation arose as to whether it might be responsible for spontaneous abortion in women. Isolated cases have suggested this. A physician wrote of a patient with a positive agglutination test who aborted twice, the placenta showing a calcified area the first time and necrotic areas full of decomposed blood clot the second time (Harris). Again, an organism culturally like the abortus bacillus appeared in the discharges of an abortion, though this did not occur in a subsequent series of 50 similar cases (Whitehouse, 1929). In another series of 48 cases in which the Wassermann reaction was negative but which were otherwise unselected, cultural examination produced the organism from only a single case, one not studied for signs of undulant fever, though specimens of the fetus or placenta or both were cultivated in all (Carpenter and Boak, 1931). The serums of 23 aborting women similarly proved negative to agglutination test with the abortus organism as antigen, though in 1 case the aborted blood gave a positive reaction (Cornell and De Young). In Gray's series of 62 women whose serums agglutinated the organism, on the other hand, 15 had had one or more abortions. The question of a relationship between spontaneous abortion and undulant fever remains open.

Pathologic changes such as those leading to abortion in cattle are not described in human cases. In the cow this inflammation is quite pronounced and characteristic. A yellowish or brown exudate forms between the uterine mucosa and the chorion; it varies in character from mucopurulent to tenacious and gluey and is composed of detritus, leukocytes and degenerating epithelial cells. The uterine mucous membrane is frequently swollen, hyperemic or hemorrhagic and is roughened by serofibrinous exudate or even shows necrotic areas (Mohler and Traum). The abortus organism invades and densely fills the epithelial cells of the chorion, and these show enlargement and vacuolation of the cytoplasm (Smith, 1919).

The study showing closest approximation to this in women antedates the discovery of undulant fever of the abortus type. It was concerned with possibilities of human contagious abortion. Three women had aborted, the fetus being expelled and the placenta removed by curet. A discharge, brownish with blood and thick, continued but

the abortus organism was not recovered (De Forest). Nothing of the sort is described in patients with undulant fever, though there has been a suggestion of the infection localizing at this site. One patient with a frank case of caprine origin aborted in the fifth month of gestation, and serum of the dead fetus showed a positive agglutination reaction (Samut). Congenital undulant fever was noted in the days of the Mediterranean Fever Commission (Williams); symptoms developed in a baby after delivery and without contact with the sick mother.

The principal morbid changes described in the female generative system involve the ovary. Oophoritis has been associated with peritoneal inflammation (Amoss and Poston). Cysts have been described: In one case they were small and hemorrhagic and located in the left ovary (Amoss, 1931) and in another they persisted so chronically as to yield a positive culture after six years (Wainwright, 1929*a*). A number of patients with undulant fever are said to have become sterile (Giordano and Ableson).

Any of the male generative organs, most often the testes, may show involvement. According to one estimate (Wainwright, 1929*b*) a mild orchitis occurs in 20 per cent of the cases of melitensis infections and in 4 per cent of those of abortus type. Testicular changes have been listed among the minor physical signs to be considered in diagnosis (Darbois, 1910). One pathologic description noted the evidence of acute interstitial orchitis and scattered areas of fibroid atrophy with vacuolar degeneration of the epithelium (Rothenberg). The epididymes may also be inflamed (Müller). Cases have been described in which prostatitis and vesiculitis, sometimes suppurative, have undoubtedly resulted from undulant fever (Simpson and Fraizer, Herbert).

Chest.—Changes in the chest are even less distinctive than those in the abdomen and usually represent complications. The pleural membrane is inflamed more often than the pericardial or peritoneal membrane. Fluid in the body cavities has been repeatedly mentioned since the earliest autopsies, usually the clear fluid of a transudate (Eyre, 1908) but often an exudate of inflammatory origin. Subsequent adhesions are not at all uncommon. Hughes (1897) encountered pleural adhesions in 6 of his cases of acute undulant fever, old adhesions in 3 and recent ones in 3. Fairly extensive obliteration of the pleural cavities is often recorded (De La Chapelle). Indication of this involvement by a homogeneous dulness in the roentgenogram (Jenkins, 1929) may find a prominent place in the clinical picture presented.

Lungs.—Bronchopneumonia readily complicates the disease, and in many cases its manifestations have been among the outstanding features. Any number of postmortem examinations have shown a greater or less degree of lobular consolidation. This occurrence, like the pleural

involvement, brings in the diagnostic roentgenogram. The film may show a general increased density and some mottling or peribronchial infiltration (Carpenter and Merriam). In certain instances the clinical manifestations have simulated tuberculosis (Bethoux). In one outbreak 15 of 75 cases of undulant fever showed pulmonary localization, and several were first recorded as tuberculosis (Vanni).

Mention is frequently made of hyperemia about the bases of the lungs; pulmonary edema is also noted. A pulmonary abscess has been described, though the authors (Hardy, Jordan, Borts and Hardy) could not determine whether it was due to the primary infection or to some secondary invasion favored by the lowering of resistance.

Heart.—The most striking of the cardiac findings is a vegetative endocarditis. This complication is encountered again and again. Hughes (1897) described vegetations on the mitral valve in 3 cases, but he thought that in one case they were probably and in the others presumably of previous origin. The more recent vegetations showed infiltration with round cells and the older ones an organization into fibrous tissue. Scott and Saphir (1928) also thought that the endocarditis they found in a case of septicemic undulant fever was probably of other causation; very likely rheumatic. The chordae tendineae of the mitral valve were thickened, shortened and adherent, and the leaflets thick, firm and covered with small, yellowish-gray, friable vegetations. The leaflets of the aortic valve were also retracted and rigid; they showed friable vegetations on their free margins and an adherent, soft, round, reddish-gray thrombus.

De La Chapelle described a vegetative and ulcerative endocarditis as being very likely the main seat of infection in a case of undulant fever and as undoubtedly caused by the organism. The two anterior cusps of the aortic valve were almost completely destroyed and replaced by a cream-colored, granular, fused mass of soft and friable vegetations partially blocking the orifice. During the four months of the disease, certain symptoms like those of a subacute streptococcic endocarditis had been noted. Others also have been inclined to think that the valvular inflammation they describe is the result of an attack of undulant fever (Heiberg; Hardy, Jordan, Borts and Hardy).

The myocardium rarely shows any significant abnormalities. Paleness is sometimes recorded and in chronic cases, fatty degeneration. In De La Chapelle's case of endocarditis it presented, besides a moderate cloudy swelling and granular degeneration of muscle fibers, a slight infiltration with large and small round cells. The blood vessels about the various sites of infective localization through the body have shown analogous cellular infiltrations. These are usually of small round cells, forming well defined aggregations in the venous wall (Wohlwill).

Thrombophlebitis has been on record so long (Cantani, 1914) and so prominently that it is surprising that deaths from emboli are not reported (Wohlwill).

Hemorrhage.—The tendency to hemorrhage is pronounced; at times it is generalized. Extravasations have been mentioned in connection with organs already described. Petechiae occur in the serous and mucous membranes and in the skin (Scott and Saphir, De La Chapelle). Bleeding is one of the clinical signs of the disease. Angle described a persistent epistaxis, ulorrhagia and hematuria, as well as a distribution of petechiae over the surface of the body. He found the bleeding time markedly prolonged, a platelet estimate of 16,000, and the clotting time three minutes.

Skin.—Changes in the skin have been frequently recorded clinically but not at autopsy. They are largely blood vascular. A roseola assumes importance because of clinical similarity between this disease and typhoid fever. Red, macular, scaling lesions, more or less distributed over the body, appear in about 5 per cent of the cases, according to Simpson and Fraizer. In some cases they present a striking resemblance to rose spots. In one case, eventually fatal, there were successive crops until by the seventh day the body was nearly covered (Duffie). An erythema multiforme has been encountered repeatedly, and once an erythema exudativum was seen (Müller). Allergic manifestations also are noted in the skin. Exposure of the hands to vaginal discharges of cows sick with contagious abortion has commonly led to an itching rash among veterinarians. This rash may consist either of irregular blotches made up of minute reddish points or of discrete red papules which in a few days change to brown (Huddleson and Johnson, 1930).

Rheumatic Symptoms.—Rheumatic symptoms enter into the disease too often to be disregarded. Some of the patients first found to have undulant fever in this country had been sent to the Army and Navy Hospital at Hot Springs for articular rheumatism (Curry). Cases have since presented symptoms in the joints with extreme frequency; a third of those in the Dayton series showed those symptoms (Simpson, 1930). In a few such cases morbid changes of the joint are definitely evident. Swelling and other signs of acute arthritis localize about a particular joint, the elbow for instance (Wellman, Eustis and Schochet). Baker isolated the organism from fluid aspirated from the knee after months of intermittent effusion into that joint. More often the condition in the joint is defined symptomatically only.

Nervous System.—Much the same might be said of the frequent neuralgic and other symptoms referable to the nervous system. In one series, with arthritis dominant, all the cases showed some such nervous symptoms: neuritis of shifting location, tremor, mental depression, exces-

sive tension or insomnia (Sensenich and Giordano). Much of this has been attributed rather indefinitely to a toxic disorder of the nervous system incidental to the general sepsis. Old cases with temporary paralyses point to some such pronounced disturbance. R. de Nunno was cited (Bassett-Smith, 1922) as stating that dead as well as living cultures of the organism produce degenerative changes of the nerve cells, with breaking up of the fibrils and leukocytic infiltration. This is less in the cord than in the cerebrum and medulla; it is marked also in the peripheral nerves. Herpes zoster has complicated the disease with implication of the posterior root ganglions of the fourth or fifth lumbar nerves (Bassett-Smith, 1920).

Bone.—Pronounced evidences of nervous disorder have been attributed in some instances to involvement of the vertebrae. Rawak and Braun cited several cases in which destructive changes of lumbar vertebrae, shown in roentgenograms, led to radiating pains in the back. In a case of their own, such pains and also atrophy of the muscles of the shoulder resulted from vertebral destruction, principally in the cervical region. Destructive changes of the vertebrae, sometimes with suppuration, are mentioned repeatedly. Trotta described suppurative changes simulating those of Pott's disease. According to Kulowski and Vinke others find both in man and in cattle an association of pronounced formation of abscesses with destructive change of the lumbar vertebrae. Abscess matter from their own case yielded a culture of the bovine organism.

Destruction of bones in undulant fever is by no means limited to the vertebral column. Weil encountered an arthritis following the disease and with it a metatarsal osteitis that caused severe swelling, pain and discoloration of the foot. Wohlwill cited Smith and Fabyan to the effect that the bone is destroyed from the marrow outward, and he therefore thought that the changes he himself saw in the marrow perhaps constituted the original osteal lesion. The pathologic structure he described consisted of small nodules like those in the spleen and lymph nodes but shaped into proliferal branches that extended along the dividing walls between droplets of fat.

Meningeal Involvement.—Occasionally the disease has been complicated by meningitis. Hansmann and Schenken carefully described one such instance in a case of undulant fever of porcine origin. The leptomeninges about the anterior and central portion of the cerebral hemispheres showed the greatest involvement, mainly along the vessels. In this region there appeared many grayish-white, tubercle-like structures. Much of the inflammatory change was obscured by hemorrhage, as a ruptured aneurysm of the basilar artery had filled the subarachnoid space at the base of the brain with blood. One of the tubercle-like

structures showed irregular masses of hyalinized connective tissue infiltrated with chronic inflammatory cells, large mononuclears surrounded by a collar of lymphocytes. Another was necrotic and contained polymorphonuclear leukocytes. The nodules were apparently proceeding from necrosis to connective tissue hyalinization. Further microscopic changes included a thickening of the pia and arachnoid membranes, with cellular infiltration and proliferation of fibrous tissue. Abundant lymphocytes, plasma cells and large mononuclears were in evidence, some of the lymphocytes appearing in perivascular accumulations. During life, the outstanding observation on the spinal fluid had been mononuclear pleocytosis, the counts recording 300 cells with 36 per cent lymphocytes and 271 cells with only 12 per cent polymorphonuclears.

Hansmann and Schenken found records of 3 proved cases of meningeal complication in the melitensis type of infection, but none prior to their own in the abortus type. Bingel and Jacobsthal subsequently reported a case in which they recovered the abortus organism from the spinal fluid. Some involvement of the brain and meninges appears to be less infrequent than one would presume from observations on encephalomeningeal reactions (Roger). Brachiofacial dysesthesia and other sensory or even motor disturbances follow a consequent irritation of the middle cerebral artery with spasms, the findings being characteristic of undulant fever. In Hughes' (1897) early series of cases of undulant fever, the meninges had been described as usually hyperemic and in some instances there was effusion into the ventricular spaces.

IMMUNE REACTIONS

The literature does not tell much about the body's natural resistance to this infection. Susceptibility to attack by the respective types of the organism differs markedly in degree, as pointed out in connection with bacteriologic observations. The lesser liability to infection during childhood is due in part to the low pathogenicity of the one type likely to reach children through milk. This protection has been attributed in part also to a lowering of susceptibility by biologic immaturity (Dietrich and Bonynge). Calves, fully exposed to the variety of the organism infective for them, exhibit the same relative immunity (Simpson, 1930).

From the first clinical observation has suggested an acquisition of at least relative immunity following an attack (Hughes, 1897). Conference of immunity by inoculation has been repeatedly and extensively tried, both prophylactically and therapeutically. The experimental use of antiserum to induce passive immunity has failed. Wright tried goat serum ineffectively and then inoculated horses, but the serum from immunized horses proved equally discouraging in various hands (Fitzgerald and Ewart; Hitchens). Current work with the serum of a goat immunized by heavy doses of vaccine detoxified with nitrous acid seems

a little more encouraging in its preliminary report (O'Neil). The dim prospect of effective serum therapy is not brightened by observations on the effect of the serums on immunized rabbits and guinea-pigs. While high titers of these serums dubiously protect guinea-pigs from experimental infection they do not at all modify the termination of an established infection (Gwatkin, 1933).

The possibility of building an active immunity by means of vaccines has been considered since the days of the Mediterranean Fever Commission (Eyre, McNaught, Kennedy and Zammit). Castellani seemed to find a prophylactic effect and incorporated selected strains of the organism of undulant fever in typhoid-paratyphoid vaccines (Castellani and Taylor). Various attempts have been made to improve the antigenic quality through the technic of preparation, as killing by chemicals instead of by heat (Gwatkin). Many have been encouraged by the results of their inoculations, vaccinated comparing favorably with nonvaccinated groups in some cases (Dubois and Sollier). Proofs of efficiency have not been widely accepted, however, for any prophylactic vaccine. This line of experimentation has brought similarly unsuccessful results with contagious abortion among cattle (Cotton, 1924).

The inadequacy of all known forms of treatment has led to extensive experimentation with therapeutic vaccines. When treatment with stock vaccine proved discouraging, the organisms obtained in blood culture were employed for inoculation (Kennedy, 1910; Owen and Newham, 1915). High hopes were aroused by early reports, but as these failed to materialize, the treatment has lost ground. Investigators still hope to produce an effective vaccine antigen. Concentration by special method and intramuscular administration have been tried (Schilling, Magee and Leitch) and the broth culture filtrate brucellin has been used, administration being gaged by phagocytic activity of the patient's cells (Huddleson and Johnson, 1933). The specific effectiveness of any immunization procedure remains to be demonstrated.

The curative effects early described are relegated more and more distinctly by subsequent work to the nonspecific. In one series of cases good results were found to follow only an intense general reaction (Cambessédès and Garnier). This led the authors to recommend large doses, and the question of a protein reaction arose. In recent years several clinicians have employed a typhoid-paratyphoid vaccine for protein shock therapy. This reduces the fever in about the same manner as the specific organism vaccines (Budtz-Olsen; Miller; Manson-Bahr, 1933).

Serologic changes of greater moment in undulant fever are the evidences of immunization that denote the infection. These have diagnostic significance far exceeding that of other clinical and laboratory findings. They were first thought to carry a practical prognostic indica-

tion as well, persistently low or declining agglutination titer of a patient's serum suggesting a bad prognosis (Birt and Lamb; Bassett-Smith, 1902).

The disease was early differentiated from others by agglutination (Wright and Smith, 1897), and this test has remainead the principal diagnostic procedure. For considerable significance the reaction must occur with the serum highly diluted. Lesser agglutination potency is acquired by the serums of many persons independently of clinical undulant fever. This was mentioned in connection with the occupational distribution of the disease, veterinarians commonly having agglutinin in their serum even to a 1:100 titer or higher (Huddleson and Johnson, 1930). This mild agglutination property has been attributed to a subclinical infection or even to the entry of organisms without infection. Continuous ingestion by monkeys of abortus organisms in small numbers results in a mild and unrecognizable yet immunizing infection (Meyer and Eddie). In one series of 500 persons with various diseases, 58 of the serums agglutinated the organism in dilutions ranging from 1:5 to 1:40 and 1 agglutinated it at 1:320 (Evans, 1925). Other series show varying degrees of agglutination similarly in 5 per cent or more (Hull and Black).

Low dilution with positive reactions may eventually assume diagnostic dependability provided a high ratio of the agglutinins is soluble in carbonic acid, according to Gray's experiments on rabbits. In animals recently immunized the specific agglutinin occurs mainly in the soluble fraction of the serum, but this portion decreases much more rapidly than that in the insoluble fraction. Scant agglutinin might therefore be attributed to an active infection if it occurs in the soluble fraction or to a previous immunizing incident if in the insoluble fraction. It seems unfortunate to disregard the low dilution reactions as largely as one now must, for a high or even a low titer of agglutination does not occur uniformly with known serum of undulant fever. A proportion of positive cases diagnosed by blood culture and serologic test fail to give the agglutination reaction just as a proportion fail to yield a blood culture of the organism (Carpenter, 1926).

Type specificity of the agglutination reaction is not at all distinct. The infecting type of the organism is likely to react to a more or less higher titer than other types. In one series of cases of caprine origin, 15 serums agglutinated the melitensis organism at 1:1,000 or 1:2,500 dilution and the remaining 4 at 1:500, while they agglutinated the abortus organism either not at all or not above 500 (Phease). De Korte's (1924) case of abortus fever gave no agglutination with the melitensis but a positive reaction with the abortus type. On the other hand, the serum in a case of undulant fever in the Rio Grande valley, contracted after drinking raw goat's milk regularly, reacted to the highest titer with

the abortus variety of the organism (Stone); a culture for typing could not be obtained. To a great extent patients' serums agglutinate indiscriminately any of the three types of organism.

Undulant fever serum is likely also to agglutinate the tularemia organism (Francis and Evans). In man and also in inoculated animals there is cross-agglutination between these two organisms, though the titer is ordinarily higher for the specific one. Occasionally patients' serums, agglutinating both at nearly equal titer, have required absorption of agglutinin for diagnosis (Carpenter, 1926). This antigenic relationship has influenced one classifier of bacteria to include the tularemia organism tentatively in the Brucella rather than the Pasteurella group (Topley and Wilson, *b*).

Immune reactions other than agglutination are readily demonstrable, though without conspicuous advantage in diagnosis. The precipitin reaction is applicable, but has nothing to recommend it over agglutination or complement fixation, except perhaps technical adaptability to the individual laboratory (Schlesmann). Complement fixation was first employed to detect infection in animals and proved as applicable to human infections, giving results generally parallel with agglutination (Larsen and Sedgwick). It becomes positive somewhat more slowly in experimentally infected goats than does the agglutination test, ten days elapsing before complete fixation takes place as against five for agglutination at 1:40 and six at 1:500 (Mohler and Eichhorn). The procedure does not overcome the outstanding errors of the agglutination test. It likewise frequently gives positive reactions in healthy persons and, according to Sedgwick and Larsen, in infants soon after they are weaned from the breast. In no respect has it proved preferable, but it is valuable for confirmation of a diagnosis when the agglutination reaction and the clinical findings conflict (Morales-Otero and Monge).

With regard to opsonic influence on phagocytosis by polymorphonuclear leukocytes, one recalls the lymphogenic character of the antigen and does not expect a great deal. A decrease is noted in the number of phagocytes and in their individual activity, but generally there is a rise in opsonin during convalescence (Bassett-Smith, 1922). In a recent paper an indication of progress toward recovery is ascribed to the phagocytic activity demonstrable in citrated samples of blood. Phagocytosis of the organism by polymorphonuclear leukocytes is thought expressive of immunity, and the lack of such activity in conjunction with a negative cutaneous reaction, of susceptibility (Huddleson, Johnson and Hamann). The reaction has been employed practically for gaging the progress of immunization (Sander).

Cutaneous hypersensitiveness to the infective agent, analogous to that in tuberculosis, was observed in guinea-pigs by Fleischner and Meyer (1918). They applied the test also to man for ruling out infection in

a series of infants. An allergic test with intradermal inoculation soon found diagnostic use (Burnet, 1922). Various antigenic preparations were used. Trenti (1923) inoculated the filtrate of a twenty day broth culture. Preference settled on a suspension of organisms from solid mediums. Giordano suspended the growth in saline solution to a density of 1 : 1,000 by silica standard, killed it by heat, injected 0.2 cc. intradermally, and looked for a local inflammatory reaction after from twelve to forty-eight hours. He obtained a pronounced positive reaction in 25 cases of undulant fever and a negative in all but 1 of 100 healthy controls. Early results showed an approximate parallel with those of agglutination (Trenti, 1925). Cross-tests between bovine and caprine strains were as strongly positive as the direct test in infected guinea-pigs (Fleischner, Meyer and Shaw) and in man (Bua).

One significant divergence in result from the serologic test appeared, in that the reaction remained positive much longer after subsidence of the active infection. Of 365 tested persons in one series, 27 who gave reason for the belief that they had or had had undulant fever gave a distinctly positive reaction to the cutaneous, but, in some instances, a negative one to the agglutination, test (Levin). Because the positive reaction fails to distinguish between present and past infection some authors attach less importance to its positive evidence of infection than to the negative evidence ruling infection out (Yeckel and Chapman). Serologic tests are preferred for the diagnosis of undulant fever, but this one confirms the doubtfully negative findings. Mallory suggests that physicians avoid the cutaneous test in presumable cases of undulant fever because it sometimes leads to a violent reaction, even to extensive necrosis (Cabot).

LABORATORY DIAGNOSIS

In view of the outstanding diagnostic value of laboratory studies on undulant fever, this review may appropriately conclude with a résumé of findings most significant in the laboratory diagnosis. First among these is the recovery and identification of the organism or its recognition by pathogenic effect on animals. Immune manifestations are nearly as significant and much more readily observable. Clinical microscopic examination adds to the initial presumption of undulant fever by means of the blood cell formula.

Of all the laboratory evidence, the observation most certainly indicative of undulant fever is recovery of the organism in culture or the infection of animals. Some permit only a tentative diagnosis on serologic test and clinical findings (Awe and Palmer). A culture is obtained most readily from the blood. The urine frequently contains organisms, though it is likely to prove positive only after repeated cultivation of samples, even with improved methods now current; the stools or some focal abscesses in exceptional instances yield the organism (Wilson,

1930). Isolation from stool demands a special technic (Amoss and Poston, 1929).

For recovery of the organism a technical procedure commonly approximated of recent years is described by Huddleson, Halsey and Torrey. They make use of liver infusion medium, control of atmosphere, differential inhibition of dye and other devices. Isolation and early cultivation too often present difficulty for the neglect of any favorable influence. Orpen suggested a method of concentration, plating the bacterial and red blood cell sediment of a centrifugated specimen. Colonies may develop within a few days and are then picked for subculture and serologic identification, but a period of two weeks or more of incubation is often required before sufficient growth develops.

The organism was first described as nonpathogenic for laboratory animals, but some years later it was found infective for rabbits and guinea-pigs (Durham). Guinea-pigs proved best suited for diagnostic inoculation; but they rarely die until after from two to three months. The animals may be killed in four or five weeks for autopsy and splenic culture (Carpenter and Boak, 1930). Infection leads to more or less characteristic change in the tissue, already described. The changes are not equally distinct with all the types and strains, and no other evidence of infection than a positive agglutination reaction of the animal's serum may appear (Cruickshank and Barbour). Infected mice yield earlier splenic culture (Hagan), and this method may offer advantages. Rainsford finds the Aleppo hamster more susceptible to infection and better adapted for diagnosis than the guinea-pig.

Among the serologic tests that of outstanding diagnostic value is agglutination. Undulant fever was among the first of the conditions to which this reaction was applied (Wright and Smith). Technical procedures were then described (Wright and Semple) adapting it for general clinical use, which it has had ever since. The serum from cases of undulant fever does not always agglutinate the organism, and that from patients without this infection may agglutinate it. Patients with severe undulant fever have had serums that were negative, or positive only at 1 : 15 or 1 : 30 (Carpenter and Boak, 1930). On the other hand, only the serum from undulant fever is at all likely to react in high dilution and it nearly always does react so. The positive agglutination test carries much more conviction if reactive to titers of 100 or above or if confirmed by culture or infection of animals. Diagnosis from less evidence than this is usual in many public health laboratories consulted by Gibbes, but is pointed out to be definitely inadequate.

Altered technical procedure has adapted the agglutination test to special situations. For immediate quantitative result the test is made on the slide, with graduated amounts of undiluted serum reacting against a standardized suspension of heated organisms in 12 per cent saline

solution; reading is from the gross flocculation that takes place (Huddleson and Abell, 1928). Bass' bedside method of agglutination for typhoid fever has likewise been adapted to undulant fever (Lewis). The "abortoscope" Bevan devised for use with cattle is also made use of, a loopful of positive blood clearing a bacterial suspension sufficiently for perception of writing through it (Ross, 1927*b*).

Since there is considerable liability to accidental infection in laboratories, the use of killed antigen stock instead of living culture assumes practical value when tests are set up by general laboratory technicians. Bevan (1921) devised a method of killing with chloroform, using his killed suspension for agglutination tests and also for vaccine. Other chemical treatments for killing and preservation find wide employment. Formaldehydized, thick milky suspensions are furnished by biologic supply houses; this stock can be diluted as required for the usual gross test. In the hands of bacteriologists, preference is sometimes expressed for the living organism as antigen (Carpenter and Boak, 1930).

The serologic test next in favor is complement fixation. This has the same disadvantages as agglutination, presenting false positive as well as false negative reactions. In one series of 1,000 unselected persons, including only 5 with known undulant fever, the complement-fixation test was positive in 96 and agglutination occurred at low dilution in 78 (Sasano, Caldwell and Medlar). Fixation may well accompany the agglutination test as a confirmatory procedure. The only serologic test to differentiate adequately between types of undulant fever is absorption of agglutinin (Carpenter and Boak, 1930).

None of the changes in the tissues are highly characteristic. Some are reflected in physical signs or in roentgenograms. The only microscopic specimen of significance is the blood smear. Others, such as sections of excised lymph glands, have rarely been considered. Differential diagnosis utilizes the blood formula principally for characteristic mononucleosis. One author suggests that while this method is not diagnostic in itself, it does advance the diagnosis from possibility to probability (Nyfeldt). Possibility of specific utilization of the blood picture is suggested by an experimental hemoclastic reaction; a specific vaccine in inoculated rabbits or in patients with undulant fever reduces the white cell count by over 1,000 cells and leads to inversion of the leukocyte formula (d'Amato, Bossa).

BIBLIOGRAPHY

d'Amato, L.: Riforma med. **44**:32, 1928.
Amoss, H. L.: Internat. Clin. **4**:93, 1931.
——and Poston, M. A.: J. A. M. A. **93**:170, 1929.
Anderson, E. D., and Pohl, J. F.: Am. J. Dis. Child. **42**:1103, 1931.
Angle, F. E. J.: Kansas M. Soc. **30**:323, 1929.
Archibald, R. G.: J. Trop. Med. **26**:55, 1923.

Atwood, G. E., and Hasseltine, H. E.: Pub. Health Rep. **45**:1343, 1930.
Aubert, P.; Cantaloube, P., and Thibault, E.: Ann. Inst. Pasteur **24**:376, 1910.
Auerbach, T.: Med. Klin. **28**:1639, 1932.
Awe, C. D., and Palmer, H. D.: Am. J. M. Sc. **176**:837, 1928.
Baastrup, V. I.: Ugesk. f. læger **90**:457, 1928.
Baker, B. M., Jr.: Arch. Int. Med. **44**:128, 1929.
Bang, B.: J. Comp. Path. & Therap. **10**:125, 1897.
Bassett-Smith, P. W.: Brit. M. J. **2**:861, 1902; **2**:324, 1904; J. Trop. Med. **17**: 93, 1914; **23**:201, 1920; Undulant Fever, in Byam, W., and Archibald, R. G.: The Practice of Medicine in the Tropics, New York, Oxford University Press, 1922, vol. 2, p. 998; Proc. Roy. Soc. Med. (jt. disc., Sects. Comp. Med., Obst. & Gynæc., & Trop. Med. & Parasitol.) **19**:13, 1926.
Bergey, D. H.: Manual of Determinative Bacteriology, ed. 4, Baltimore, Williams & Wilkins Company, 1933.
Bethoux, L.: Presse méd. **37**:835, 1929.
Bevan, L. E. W.: Tr. Roy. Soc. Trop. Med. & Hyg. **15**:215, 1921; Proc. Roy. Soc. Med. (jt. disc., Sects. Comp. Med., Obst. & Gynæc., & Trop. Med. & Parasitol.) **19**:8, 1926.
Bierring, W. L.: J. A. M. A. **93**:897, 1929.
Bingel, A., and Jacobsthal, E.: Klin. Wchnschr. **12**:1093, 1933.
Birt, C., and Lamb, G.: Lancet **2**:701, 1899.
Blake, F. G., and Oard, H. C.: Yale J. Biol. & Med. **1**:128, 1929.
Blanchard, R.: Bull. Acad. de méd., Paris **65**:181, 1911.
Blumer, G.: Ann. Int. Med. **3**:122, 1929.
Bossa, G.: Riforma med. **45**:211, 1929.
Boyd, W.: A Textbook of Pathology, Philadelphia, Lea & Febiger, 1932.
Broadbent, W.: Lancet **1**:76, 1931.
Bruce, D.: Practitioner **39**:161, 1887; **40**:241, 1888; Brit. M. J. **1**:1101, 1889.
Bua, F.: Policlinico (sez. prat.) **34**:631, 1927.
Budtz-Olsen, J.: Ugesk. f. læger **92**:596, 1930.
Burnet, E.: Compt. rend. Acad. d. sc. **174**:421 and 973, 1922; **187**:545, 1928.
Cabot, R. C.: New England J. Med. **208**:1317, 1933.
Cambessédès, H., and Garnier, G.: Paris méd. **1**:281, 1929.
Cantani, A.: Policlinico (sez. prat.) **21**:741, 1914.
Carey, J. D., and Newsom, I. E.: Colorado Med. **26**:320, 1929
Carpenter, C. M.: J. Infect. Dis. **39**:220, 1926; J. Am. Vet. M. A. **70**:459, 1927.
——and Boak, Ruth: Am. J. Pub. Health **18**:743, 1928; J. Lab. & Clin. Med. **15**:437, 1930; J. A. M. A. **96**:1212, 1931; Am. J. M. Sc. **185**:97, 1933.
——and Merriam, H. E.: J. A. M. A. **87**:1269, 1926.
Castellani, A., and Taylor, F.: Brit. M. J. **2**:356, 1917.
Clark, R. H.: New Orleans M. & S. J. **85**:737, 1933.
Clouston, H. R.: Canad. M. A. J. **28**:535, 1933.
Cornell, E. L., and De Young, C. R.: Am. J. Obst. & Gynec. **18**:840, 1929.
Cotton, W. E.: J. Am. Vet. M. A. **62**:179, 1922; Vet. Med. **19**:463, 1924.
Craig, C. F.: Am. J. M. Sc. **125**:105, 1903; Internat. Clin. **4**:89, 1906.
Cruickshank, J. N., and Cruickshank, R.: Brit. M. J. **1**:195, 1930.
Cruickshank, R., and Barbour, W. J.: Lancet **1**:852, 1931.
Curry, J. J.: J. M. Research **6**:241, 1901.
Dalrymple-Champneys, W.: Brit. M. J. **2**:604, 1931; Proc. Roy. Soc. Med. **26**: 1093, 1933.
Darbois, P.: Presse méd. **18**:923, 1910.
De Forest, H. P.: Am. J. Obst. & Gynec. **76**:221, 1917.

De La Chapelle, C. E.: Am. Heart J. **4**:732, 1929.
Demaree, E. W.: Kentucky M. J. **31**:343, 1933.
Dietrich, H., and Bonynge, C. W.: J. Pediat. **1**:46, 1932.
Dubois, C., and Sollier, N.: Ann. Inst. Pasteur **45**:596, 1930.
Duffie, D. H.: J. A. M. A. **87**:1830, 1926.
Duncan, J. T.: Tr. Roy. Soc. Trop. Med. & Hyg. **22**:269, 1928.
Durham, H. E.: J. Path. & Bact. **5**:377, 1898.
Evans, A. C.: (*a*) J. Infect. Dis. **22**:580, 1918; (*b*) ibid. **23**:354, 1918; (*c*) U. S. Pub. Health Service, Hygienic Lab. Bull. no. 143, 1925; (*d*) J. A. M. A. **88**:630, 1927.
Eyre, J. W. H.: J. Roy. Army M. Corps **8**:113, 1907; Lancet **1**:1747, 1908; **1**:88, 1912; Proc. Roy. Soc. Med. (jt. disc., Sect. Comp. Med., Obst. & Gynæc., & Trop. Med. & Parasitol.) **19**:1, 1926.
——and Fawcett, J.: Guy's Hosp. Rep. **59**:209, 1905.
——McNaught, J. G.; Kennedy, J. C., and Zammit, T.: Great Britain Mediterranean Fever Commission Reports, London, Harrison & Sons, 1907, pt. 6, p. 130.
Ferenbaugh, T. L.: J. A. M. A. **57**:730, 1911.
Feusier, M. L., and Meyer, K. F.: J. Infect. Dis. **27**:185, 1920.
Fitzgerald, E. D., and Ewart, J. H.: Lancet **1**:1924, 1899.
Fleischner, E. C., and Meyer, K. F.: Am. J. Dis. Child. **14**:157, 1917; **16**:268, 1918.
——Meyer, K. F., and Shaw, E. B.: ibid. **18**:577, 1919.
——Vecki, M.; Shaw, E. B., and Meyer, K. F.: J. Infect. Dis. **29**:663, 1921.
Francis, E.: Pub. Health Rep. **46**:2416, 1931.
——and Evans, A. C.: Pub. Health Rep. **41**:1273, 1926.
Gallagher, J. R.: Am. J. M. Sc. **185**:391, 1933.
Gentry, E. R.: Undulant Fever, in Christian, H. A.: Oxford Medicine, New York, Oxford University Press, 1930, vol. 4, p. 799.
——and Ferenbaugh, T. L.: J. A. M. A. **57**:889 and 1045, 1911.
Gibbes, J. H.: South. M. J. **24**:126, 1931.
Gilbert, R., and Coleman, M. B.: J. Infect. Dis. **43**:273, 1928.
Giordano, A. S.: J. A. M. A. **93**:1957, 1929.
——and Ableson, Marjorie: J. A. M. A. **92**:198, 1929.
Good, E. S., and Smith, W. V.: J. Bact. **1**:415, 1916.
Gray, J. D. A.: J. Bact. **25**:415, 1933.
Great Britain Mediterranean Fever Commission Reports, London, Harrison & Sons, pts. 1, 2 and 3, 1905; pt. 4, 1906; pts. 5, 6 and 7, 1907.
Gregersen, F., and Lund, T. M.: Hospitalstid. **74**:349, 1931.
Griffin, W. A.: New England J. Med. **202**:324, 1930.
Gwatkin, R.: J. Infect. Dis. **48**:381, 1931; **53**:230, 1933.
Hagan, W. A.: J. Exper. Med. **36**:727, 1922.
Hansmann, G. H., and Schenken, J. R.: Am. J. Path. **8**:435, 1932.
Hardy, A. V.: (*a*) Pub. Health Rep. **43**:2459, 1928; (*b*) J. A. M. A. **92**:853, 1929; (*c*) **93**:891, 1929.
——Jordan, C. F.; Borts, I. H., and Hardy, G. C.: Nat. Inst. Health Bull. no. 158, 1931.
Harris, H. J.: J. A. M. A. **101**:1584, 1933.
Hasseltine, H. E.: Pub. Health Rep. **44**:1659, 1929; **45**:1660, 1930; **46**:1519, 1931.

Heiberg, S.: Hospitalstid. **73**:933, 1930.
Herbert, L. A.: New Orleans M. & S. J. **84**:259, 1931.
Hill, O. W., and Monger, R. H.: J. A. M. A. **97**:176, 1931.
Hislop, J. A.: Brit. M. J. **2**:870, 1902.
Hitchens, A. P.: Am. J. Trop. Dis. **1**:228, 1913.
Holt, R. F., and Reynolds, F. H. K.: Mil. Surgeon **56**:414, 1925.
Huddleson, I. F.: J. A. M. A. **86**:943, 1926; J. Bact. **17**:58, 1929; Am. J. Pub. Health **21**:491, 1931.
——and Abell, E.: J. Bact. **13**:13, 1927; J. Infect. Dis. **42**:242, 1928.
——and Hallman, E. T.: J. Infect. Dis. **45**:293, 1929.
——Halsey, D. E., and Torrey, J. P.: J. Infect. Dis. **40**:352, 1927.
——and Johnson, H. W.: J. A. M. A. **94**:1905, 1930; Am. J. Trop. Med. **13**:485, 1933.
——Johnson, H. W., and Hamann, E. E.: Am. J. Pub. Health **23**:917, 1933.
Hughes, M. L.: Lancet **2**:238, 1896; Mediterranean, Malta or Undulant Fever, New York, The Macmillan Company, 1897.
Hull, T. G., and Black, L. A.: J. A. M. A. **88**:463, 1927.
Jenkins, P. K.: J. A. M. A. **92**:1593, 1929.
Jordan, C. F.: J. Infect. Dis. **48**:526, 1931.
Kampmeier, R. H.: Am. J. M. Sc. **176**:177, 1928.
Keefer, C. S.: Bull. Johns Hopkins Hosp. **35**:6, 1924.
Kennedy, J. C.: J. Roy. Army M. Corps **15**:317, 1910; **22**:9, 1914.
Kern, R. A.: Am. J. M. Sc. **176**:405, 1928.
King, W. F.: J. A. M. A. **91**:552, 1928.
Kohlbry, C. O.: Minnesota Med. **12**:414, 1929.
de Korte, W. E.: South African M. Rec. **22**:478, 1924.
Kristensen, M.: Ugesk. f. læger **90**:869, 1928.
——Helms, T., and Martensson, A.: Ugesk. f. læger **93**:51, 1931.
Kulowski, J., and Vinke, T. H.: J. A. M. A. **99**:1656, 1932.
Lake, G. C.: Pub. Health Rep. **37**:2895, 1922.
Larsen, W. P., and Sedgwick, J. P.: Am. J. Dis. Child. **6**:326, 1913.
Leavell, H. R.; Poston, M., and Amoss, H. L.: Arch. Int. Med. **48**:1186, 1931.
Lehmann, K. B., and Neumann, R. O.: Determinative Bacteriology, New York, G. E. Stechert & Company, 1931, vol. 2.
Levin, W.: J. Lab. & Clin. Med. **16**:275, 1930.
Lewis, S. J.: New Orleans M. & S. J. **83**:26, 1930.
Loewy, I. D.: U. S. Vet. Bur. M. Bull. **6**:635, 1930.
Löffler, W.: Schweiz. med. Wchnschr. **59**:304, 1929.
McAlpine, J. G., and Mickle, F.: Am. J. Pub. Health **18**:609, 1928.
——and Slanetz, C. A.: J. Infect. Dis. **42**:66 and 73, 1928.
McCulloch, T.; Weir, J. C., and Clayton, F. H. A.: Great Britain Mediterranean Fever Commission Reports, London, Harrison & Sons, 1907, pt. 7, pp. 74 and 218.
McFadyean, J., and Stockman, S.: J. Comp. Path. & Therap. **22**:264, 1909.
MacNeal, W. J., and Kerr, J. E.: J. Infect. Dis. **7**:469, 1910.
Manson-Bahr, P.: Lancet **1**:1178, 1933.
——and Willoughby, H.: Brit. M. J. **1**:633, 1929.
Marr, D. M.: Brit. M. J. **1**:959, 1933.
Marston, J. A.: Great Britain Army Medical Reports of 1861, p. 486.

Mason, C. F.: New York M. J. **78**:267, 1903.
Mason, E. M.: J. M. A. Alabama **1**:50, 1931.
Melvin, A. D.: U. S. Dept. Agric., Bur. Animal Ind., circ. 198, 1912.
Meyer, K. F., and Eddie, B.: Proc. Soc. Exper. Biol. & Med. **27**:222, 1929.
——and Shaw, E. B.: J. Infect. Dis. **27**:173, 1920.
Miller, S.: Lancet **1**:1177, 1933.
Mohler, J. R., and Eichhorn, A.: J. A. M. A. **58**:1107, 1912.
——and Traum, J.: Ann. Rep. Bur. Animal Ind., 1911, p. 147.
Moorehead, M. T.: M. Bull. Vet. Admin. **8**:195, 1932.
Morales-Otero, P.: Puerto Rico J. Pub. Health & Trop. Med. **5**:144, 1929; J. Infect. Dis. **52**:54, 1933.
——and Monge, G.: Puerto Rico J. Pub. Health & Trop. Med. **8**:193, 1932.
Muir, Robert: A Textbook of Pathology, New York, Longmans, Green & Co., 1931, p. 440.
Müller, L. R.: München. med. Wchnschr. **78**:1813, 1931.
Nyfeldt, A.: Ugesk. f. læger **92**:491, 1930.
O'Neil, A. E.: Ohio State M. J. **29**:438, 1933.
Orpen, L. J. J.: South African M. Rec. **21**:325, 1923.
Owen, S. A., and Newham, H. B.: Lancet **2**:536, 1915.
Phease, R. N.: J. Roy. Army M. Corps **61**:296, 1933.
Rainsford, S. G.: Irish J. M. Sc. **88**:150, 1933.
Rawak, F., and Braun, R.: Klin. Wchnschr. **10**:776, 1931.
Rodriguez de Partearroyo, F.: Siglo méd. **76**:53, 1925.
Rössle, R.: München. med. Wchnschr. **80**:5, 1933.
Roger, H.: Marseille-méd. **68**:727, 1931.
Ross, E. H.: J. Trop. Med. **9**:17, 1906.
Ross, G. R.: (*a*) J. Hyg. **26**:403, 1927; (*b*) Tr. Roy. Soc. Trop. Med. & Hyg. **21**:57, 1927.
Rothenberg, R. C.: Ann. Int. Med. **6**:1275, 1933.
Samut, R.: Lancet **2**:878, 1911.
Sander, J. F.: J. Michigan M. Soc. **32**:109, 1933.
Sasano, K. T.; Caldwell, D., and Medlar, E. M.: J. Infect. Dis. **48**:576, 1931.
Schilling, G. S.; Magee, C. F., and Leitch, F. M.: J. A. M. A. **96**:1945, 1931.
Schlesmann, C.: Klin. Wchnschr. **11**:1711, 1932.
Schottmüller, H.: Deutsche med. Wchnschr. **56**:1813, 1930.
Schroeder, E. C., and Cotton, W. E.: Am. Vet. Rev. **40**:195, 1911.
Scott, R. W., and Saphir, O.: Am. J. M. Sc. **175**:66, 1928.
Sedgwick, J. P., and Larsen, W. P.: Am. J. Dis. Child. **10**:197, 1915.
Sensenich, R. L., and Giordano, A. S.: J. A. M. A. **90**:1782, 1928.
Sergent, E.; Gillot, V., and Lemaire, G.: Ann. Inst. Pasteur **22**:209, 1908.
Simpson, W. M.: Ann. Int. Med. **4**:238, 1930; South. Surgeon **1**:184, 1932.
——and Fraizer, E.: J. A. M. A. **93**:1958, 1929.
Smith, T.: J. Exper. Med. **29**:451, 1919; **43**:207, 1926; Medecine **8**:193, 1929.
Starr, L. E., and Maxcy, K. F.: Virginia M. Monthly **60**:218, 1933.
Stone, C. T.: Texas State J. Med. **25**:225, 1929.
Strong, R. P.: Undulant Fever, in Nelson Loose-Leaf Living Medicine, New York, Thomas Nelson & Sons, 1931, vol. 2, p. 209.
——and Musgrave, W. E.: Philadelphia M. J. **6**:996, 1909.
Tappau, J. W.: Texas State J. Med. **19**:176, 1923.

Thompson, A.: Irish J. M. Sc. **72**:655, 1931.
Thompson, R.: Canad. M. A. J. **29**:9, 1933.
Tilghman, S. J.: Delaware State M. J. **5**:156, 1933.
Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, New York, William Wood & Company, 1929, (*a*) p. 1116; (*b*) p. 509.
Trenti, E.: Policlinico (sez. med.) **30**:1249, 1923; ibid. (sez. prat.) **32**:767, 1925.
Trotta, G.: Wien. klin. Wchnschr. **26**:1395, 1913.
Tyndale, W. R., and Viko, L. E.: J. A. M. A. **81**:1953, 1923.
Vanni, V.: Riforma med. **41**:555, 1925.
Wade, E.: Lancet **1**:1342, 1933.
Wainwright, C. W.: (*a*) Bull. Johns Hopkins Hosp. **45**:133, 1929; (*b*) South. M. J. **22**:1049, 1929.
Watkins, W. W., and Lake, G. C.: J. A. M. A. **89**:1581, 1927.
Weigmann, F.: Arch. f. Hyg. **102**:77, 1929.
Weil, S.: Zentralbl. f. Chir. **57**:1269, 1930.
Wellman, C.; Eustis, A., and Schochet, S. S.: Am. J. Trop. Dis. **1**:393, 1913.
Whitehouse, B.: Brit. M. J. **2**:1095, 1929.
Widal, F.; Léon-Kindberg, and Cotoni: Bull. Acad. de méd., Paris **64**:328, 1910.
Williams, E. M.: J. Roy. Army M. Corps **9**:59, 1907.
Wilson, G. S.: Brit. M. J. **2**:679, 1930; Bull. Hyg. **6**:389, 1931.
Winslow, C. E. A.; Broadhurst, J.; Buchanan, R. E.; Krumwiede, C.; Rogers, L. A., and Smith, G. H.: J. Bact. **5**:191, 1920.
Wohlwill, F.: Virchows Arch. f. path. Anat. **286**:141, 1932.
Wright, A. E., and Semple, D.: Brit. M. J. **1**:1214, 1897.
——and Smith, F.: Lancet **1**:656, 1897.
Yeckel, H. C., and Chapman, O. D.: J. A. M. A. **100**:1855, 1933.
Yount, C. E., and Looney, R. N.: Arizona M. J. **1**:18, 1913.

News and Notes

University News, Promotions, Resignations, Appointments, Deaths, etc.—Ulrik Quensel, emeritus professor of pathology in the University of Uppsala, Sweden, has died at the age of 71.

The knighthood of the Order of the British Empire has been conferred on Frederick G. Banting of the University of Toronto.

M. G. Ramon, chief of the veterinary service of the Pasteur Institute, has been appointed subdirector of the institute. Dr. Ramon succeeds to the chair at the Academy of Medicine occupied by the late Emile Roux.

Hans Zinsser will spend the second half of the academic year 1934-1935 as an exchange professor at the University of Paris from Harvard University.

John A. Kolmer has been elected director of the Research Institute of Cutaneous Medicine in Philadelphia.

Louis Martin, chief of the serotherapeutic service of the Pasteur Institute in Paris, has been appointed director of the institute. Dr. Martin has been associated with the institute for forty years.

William Snow Miller, emeritus professor of anatomy at the University of Wisconsin, received the Trudeau medal at the thirtieth annual meeting of the National Tuberculosis Association in Cincinnati.

Journal of the Mount Sinai Hospital, New York.—This journal will be devoted principally to case reports. From time to time formal annual lectures delivered at the hospital may be included. The first number has been published.

Mary Putnam Jacoby Fellowship.—The Women's Medical Association of New York City announces that this fellowship ($1,000 for one year) is open for investigative work in the medical sciences to women who are graduates of approved medical schools. Applications for 1934-1935 should be filed with Dr. Rose Cohen, 36 West Ninetieth Street, New York, not later than Sept. 1, 1934. With the applications should go statements as to health, educational qualifications and problems for investigation.

Library of Legal Medicine.—According to the Harvard Alumni Bulletin there has been established in the department of legal medicine of the Harvard Medical School a library of legal medicine. The department and library owe their existence to the generosity of Mrs. Frances Glessner Lee and bear the name of George Burgess Magrath, the present professor of legal medicine and a medical examiner for Suffolk County, Boston.

Medals of Scientific Exhibit.—The gold medal of the Scientific Exhibit of the American Medical Association at its last meeting, in Cleveland, was awarded to Gregory Shwartzman, Mount Sinai Hospital, New York, for his original investigations of skin reactivity to bacterial filtrates, its rôle in immunology and its practical applications. The silver medal was awarded to Timothy Leary, medical examiner for Suffolk County, Boston, for original work on the relation of cholesterol to atherosclerosis.

Society News.—The American College of Physicians will meet in Philadelphia on April 29 to May 3, 1935.

The ninth congress of the Far Eastern Association of Tropical Medicine will be held in Nanking on Oct. 1 to 7, 1934. The secretary of the executive committee is Dr. P. Z. King, National Health Administration, Nanking, China.

The Neisserian Medical Society of Massachusetts is composed of some seventy physicians who are interested especially in gonorrhea. The official organ of the society is the *New England Journal of Medicine*. The object of the society is to give members of the medical profession the benefit of the experience of the specialist in gonococcic infection.

Abstracts from Current Literature

Pathologic Anatomy

CONGENITAL ANOMALIES OF THE CORONARY ARTERIES WITH CARDIAC HYPERTROPHY. E. F. BLAND, P. D. WHITE and J. GARLAND, Am. Heart J. **8**:787, 1933.

A male infant who died at the age of 3 months showed an abnormal origin of the left coronary artery from the pulmonary artery, associated with marked enlargement of the heart (due to hypertrophy and dilatation of the left ventricle) and extensive degenerative changes in the ventricular wall supplied by the malposed vessel. In view of these findings it is probable that the paroxysmal attacks of acute discomfort precipitated by exertion and associated with profound vasomotor collapse occurring in this infant were those of angina pectoris. The electrocardiographic picture was similar to that of an adult with severe coronary disease. In the few recorded cases of this rare anomaly (eight in addition to the one reported in this article) a characteristic pathologic picture has resulted. Death within the first year has been the rule. Two of the cases have been exceptional.

AUTHORS' SUMMARY.

ANOMALOUS ORIGIN OF THE LEFT CIRCUMFLEX CORONARY ARTERY. WILLIAM ANTOPOL and M. A. KUGEL, Am. Heart J. **8**:802, 1933.

Four hearts were studied in which there were an anomalous origin and course of the left circumflex coronary artery. In each heart the left anterior descending branch and the right coronary artery had their normal origin and distribution. In three hearts the left circumflex coronary artery arose directly from the right sinus of Valsalva, immediately posterior to the origin of the right coronary artery. It then pursued its course posteriorly to the root of the aorta and the left auricular appendage around the margo obtusus in the auriculoventricular sulcus. In the fourth case the left circumflex coronary artery arose as a branch of the right coronary artery 1 cm. from its ostium. It then maintained a course similar to that described for the left circumflex coronary artery in the other three cases. A point of clinical interest in one of these cases is the fact that the left circumflex coronary artery was normal and patent throughout, whereas the right coronary artery and the left anterior descending branch presented numerous occlusions. The clinical history of the 51 year old patient gave ample evidence of repeated attacks of coronary occlusion in the last three years of his life. It seems possible that the independent origin and distribution of the left circumflex coronary artery in this case served for a time as a compensating source of nutrition to the myocardium through its anastomoses.

AUTHORS' SUMMARY.

LUNGS AFTER TREATMENT OF ASPHYXIA NEONATORUM IN THE DRINKER RESPIRATOR. D. P. MURPHY and J. T. BAUER, Am. J. Dis. Child. **45**:1196, 1933.

The pathologic changes in the lungs of thirty asphyxiated infants who were given artificial respiration in the Drinker respirator, but who died within twenty-four hours after birth, are compared with those in a similar number who had not received this means of artificial respiration. Seventy per cent of the thirty deaths were the result of either intracranial injury or prematurity. No death was due to a pulmonary condition. A slight increase in the incidence of pulmonary congestion followed the use of the Drinker respirator; this indicated that the treatment had an appreciable effect on the contents of the chest. Artificial respiration had no influence on the kind of cellular elements observed in the air passages, but

may have drawn amniotic débris from the bronchioles to the alveoli. Otherwise, no gross or microscopic changes were recognized in the lungs of the treated infants that had not been seen in the lungs of untreated infants.

AUTHORS' SUMMARY.

"DOUBLE APPENDIX" ASSOCIATED WITH OTHER CONGENITAL ANOMALIES. HENRY N. PRATT, Am. J. Dis. Child. **45**:1263, 1933.

Because of an imperforate anus, sigmoidostomy was performed on a boy born at full term, who died fifteen days later, after a course of septic fever. Necropsy revealed mesenteric attachments of the midline embryonic type. The rectum was congenitally absent, while the sigmoid ended in a blind pouch at the base of the posterior aspect of the bladder. The sigmoid was represented by one small loop of fused bowel with a continuous lumen. Above the pouchlike sigmoid was about 7 cm. of intestinal tract, presumably colon, stretching upward and somewhat to the right. At this point there were two "appendixes" on opposite sides of a slight fusiform swelling, presumably the cecum, each having an individual mesenteric attachment to the ileum. Two lateral taeniae on the colon terminated at the bases of the "appendixes." The ileum was directly continuous with, and had practically the same caliber as, the preceding colon. Above the colon the enteric tract appeared to be normal. Pratt points out that the anomalous character of the enteric tract in this case is suggestive of avian morphology.

RALPH FULLER.

ATELECTASIS OF THE NEW-BORN. SIDNEY FARBER and JAMES L. WILSON, Am. J. Dis. Child. **46**:572, 1933.

A certain degree of initial atelectasis is physiologic for probably several days after birth. In this type of unexpanded lung the alveoli are small, circular and lined with cuboid epithelium. In the lungs of infants who have lived several days areas of resorption atelectasis may be demonstrable. In these areas the collapsed alveoli present tortuous walls and are lined by flattened cells. In premature infants there may be solid areas of pulmonary parenchyma superficially resembling atelectasis but explained by incomplete development or immaturity of these areas.

RALPH FULLER.

ENDOMETRIOSES OF LYMPH NODES. G. H. HANSMANN and J. R. SCHENKEN, Am. J. Obst. & Gynec. **25**:572, 1933.

In two cases endometrial tissue was found in the regional lymph nodes of the uterus post mortem. One of the patients had had a syncytioma malignum in which endometrial tissue may have entered the lymphatics. The vessels of the endometrium are opened during menstruation. Viable endometrial tissue has been found free in the oviducts as well as in the venous sinuses and the lymphatic vessels of the uterus.

JACOB KLEIN.

THE MICROINCINERATION OF HERPETIC INTRANUCLEAR INCLUSIONS. L. E. RECTOR and E. J. RECTOR, Am. J. Path. **9**:587, 1933.

Microscopic examination of incinerated herpetic intranuclear inclusions from the cerebral cortex of rabbits reveals the presence of considerable inorganic material in young full inclusions with a progressive decrease in amount as the inclusions develop. Mature inclusions are frequently devoid of any inorganic residue.

AUTHORS' SUMMARY.

RARE FORM OF SACCULAR CARDIAC ANEURYSM WITH SPONTANEOUS RUPTURE. W. C. HUNTER and R. L. BENSON, Am. J. Path. **9**:593, 1933.

A man, 45 years old, died suddenly of spontaneous rupture of the thin fibrous wall of an aneurysm of the external aspect of the left ventricle. The wall of the

aneurysm varied between 0.1 and 0.7 cm. in thickness; the aneurysm appeared to have originated in a small area of myocardial fibrosis.

CONTROLLED FORMATION OF COLLAGEN AND RETICULUM. S. BURT WOLBACH, Am. J. Path. **9**:689, 1933.

Fibrin and other preformed materials do not contribute to collagen formation in repair by organization. Collagen and reticulum are physical variations of the same material. Collagen is the product of the secretory activity of fibroblasts, and its alinement and distribution are determined by the shape of the cell and its processes, including fibroglia fibrils. AUTHOR'S CONCLUSIONS.

THE HISTOPATHOLOGY OF THERAPEUTIC (TERTIAN) MALARIA. WALTER L. BRUETSCH, Am. J. Psychiat. **12**:19, 1932.

The immediate tissue reaction of the body to the malarial plasmodium consists in a stimulation of the reticulo-endothelial apparatus (system of histiocytes), leading to a new formation of macrophagic tissue in various organs. Both the specific endothelia of the liver, spleen, lymph nodes and bone marrow and the histiocytes of the connective tissue take part in the stimulation. In therapeutic malaria the histiocytes of the blood are mainly derivatives of the specific endothelium. To a minor degree, common capillary endothelium is engaged in the formation of intravascular endothelial phagocytes. This has been established for the endothelium of the capillaries of the cortex of the brain and for the endothelial cells of the capillary venules of certain connective tissues. By means of the supravital technic, it has been found that the intravascular macrophagic phagocytes are clasmatocytes in the sense of Sabin, Doan and Cunningham. Although the capillary endothelial cells show signs of stimulation, they do not become phagocytic while they retain their anatomic position in the walls of the vessels.

In addition to involvement of the histiocytes, there is an activation of the undifferentiated embryonic mesenchymal cells. The fibroblast, the mesothelial cell and the histiocyte are distinct types of cells. While both the fibroblast and the mesothelial cell are also capable of stimulation, they can be distinguished from the active histiocyte in malaria-infected tissue.

In the nervous system the macrophagic response has been greatest in the leptomeninges. In the arachnoid the malaria-stimulated histiocytes stand out distinctly from the less active arachnoid lining cell. In the adventitial sheaths of the vessels of the cortex of the brain the mesodermal phagocytes are only slightly stimulated. A small increase in the number of macrophages has been found about middle-sized and large cortical vessels. Stimulated histiocytes are more numerous in the perivascular spaces of the large vessels in the white matter, and in the striatum and pons. The small mesodermal elements along the capillaries of the cortex of the brain have not been seen to be activated. The microglia, as a whole, do not take part in the general reaction of the reticulo-endothelial system.

Therapeutic malaria produces an activation of the mesodermal tissue in which stimulation of the histiocytes and activation of the undifferentiated mesenchymal cells are outstanding features. AUTHOR'S SUMMARY.

THE PATHOLOGICAL ANATOMY OF PULMONARY TUBERCULOSIS IN THE AMERICAN NEGRO AND IN THE WHITE RACE. FRANKLIN R. EVERETT, Am. Rev. Tuberc. **27**:411, 1933.

The anatomic characteristics of tuberculosis differ widely in American Negroes and white persons of the same community in that the disease pursues a more rapidly fatal course in the Negroes and more frequently takes the form of a widespread pneumonia with rapid excavation of the lung and less conspicuous formation of fibrous tissue. The type of pulmonary tuberculosis which is prevalent in adult white persons occurs in only half of the Negroes who contract pulmonary tuber-

culosis and pursues in them a more rapid course. The type of pulmonary tuberculosis characteristic of childhood, with caseous tracheobronchial lymph nodes, occurs in nearly 50 per cent of adult Negroes, but in only a small percentage of adult white persons who die of pulmonary tuberculosis. In more than half of the adult Negroes with the childhood type of pulmonary tuberculosis the lesion has its origin in the apex of the lung. Latent apical tuberculosis occurs considerably less frequently in adult Negroes than in adult white persons. H. J. CORPER.

FATTY INFILTRATION OF THE MYOCARDIUM. O. SAPHIR and M. CORRIGAN, Arch. Int. Med. **52**:410, 1933.

By fatty infiltration of the myocardium is meant the formation of an abundance of subepicardial fat which extends into the myocardium and occupies the usual position of the muscle fibers. A short review of the literature on fatty infiltration of the myocardium is given, and a study of fifty-eight cases is reported. The myocardium of the right ventricle is the region mainly affected. The infiltration leads to a replacement of the muscle fibers by fatty tissue. The muscle fibers primarily become atrophic and later apparently disappear. If the replacement by fat involves a large portion of the myocardium it may lead to sudden death. Only if careful autopsy reveals the absence of all other major lesions may fatty infiltration of the myocardium be regarded as the sole cause of death.

Two cases of this type are reported. In two other cases replacement of the myocardium by fat was in all probability the cause of death. In one the diagnosis was pseudohypertrophic muscular dystrophy in which the fatty infiltration of the myocardium was probably a part of the general replacement of muscle with fat. In the second the patient died after partial thyroidectomy. In twenty-nine instances other pathologic changes, in addition to fatty infiltration of the myocardium, were found at autopsy. In these cases the lesion in the heart was thought to be a factor in hastening death. In twenty-five instances fatty infiltration of the myocardium was an incidental finding at autopsy. A clinical study of the patients whose cases are reported reveals that fatty infiltration of the myocardium may cause death without any premonitory symptoms of heart failure. When such infiltration is present, factors which cause an increased demand on the heart and which under normal conditions could easily be compensated for may lead to sudden death. Fatty infiltration of the myocardium may be regarded as a morphologically demonstrable cause of heart failure and death in instances in which death clinically was thought to have been the result of functional disorders without a morphologic basis. Further study with exact clinical methods might establish a complex of signs and symptoms sufficiently characteristic to warrant a clinical diagnosis of fatty infiltration of the myocardium. AUTHORS' SUMMARY.

THROMBOSIS OF INTRACRANIAL ARTERIES. H. H. HYLAND, Arch. Neurol. & Psychiat. **30**:342, 1933.

Hyland records three cases in which the clinical and pathologic features were peculiar. In the first, necropsy revealed thrombosis of both anterior cerebral arteries which was clinically manifested by complete paralysis of the left leg, partial paralysis of the left arm, apraxia and a grasp reflex. There were also mental disturbances—euphoria, freedom from inhibitions and motor activity in the nonparalyzed extremities ("the arm, for instance, was in a constant state of purposeful activity, grasping at anything that came within reach"). In the second case there were sudden weakness in the left extremities, hypotonia, active tendon reflexes, diplopia and dysphagia. The pathologic diagnosis was: thrombosis of the left vertebral and basilar arteries, cerebral arteriosclerosis and acute sphenoid sinusitis. No evidence of syphilis was found, though the Wassermann reaction was 4+. In case 3 the clinical signs were: sudden flaccid hemiplegia on the left side, blindness in the right eye and failure of its pupil to react to light, and sensory disturbances over the paralyzed face and arm. There were thrombosis of the

central artery of the retina and of the right carotid and middle cerebral arteries, softening of the parts of the brain supplied by the latter and demyelinization of the right optic nerve.

G. B. HASSIN.

FAMILIAL SPASTIC PARALYSIS. HARRY A. PASKIND and THEODORE T. STONE, Arch. Neurol. & Psychiat. **30**:481, 1933.

Whereas spastic paraplegia involving the lower extremities only or both the lower and upper extremities, with or without bulbar and mental manifestations, has repeatedly been described from the clinical standpoint (in 152 families), histologic reports are exceedingly rare. The patient of Paskind and Stone was one of five siblings. Of these, two brothers were also afflicted with spastic paraplegia, and all three were idiots; one other brother and a sister, aged 9 months, were normal. The remarkable macroscopic features were: complete absence of sulci and convolutions over the parietal and occipital lobes except at the tips of the latter, numerous brown areas of gray matter within the white substance (heterotopia) and defective myelinization, especially in the white matter of the occipital and parietal lobes. The spinal cord showed no changes. In the parietal and occipital lobes the defective myelinization was associated with agyria—the structures regulating motion and acting as cortical receptors for sensation were not developed. The extrapyramidal fibers were normal. Absence of association fibers in the parietal and occipital lobes had resulted in pachygyria.

G. B. HASSIN.

ANEURYSM OF THE INTERNAL CAROTID ARTERY. ROBERT ZOLLINGER and ELLIOTT C. CUTLER, Arch. Neurol. & Psychiat. **30**:607, 1933.

A patient presented symptoms and signs of involvement of the second, third, fourth, fifth, seventh and eighth cranial nerves on the right and an enlarged sella turcica, with destruction of the clinoid processes. The condition proved to be due to an aneurysm of the right carotid artery, which had eroded the sphenoid and temporal bones, infringed on the sella turcica, become adherent to the fourth and fifth nerves and displaced the other cranial nerves. The pituitary gland was not grossly identified and was apparently a part of the aneurysmal wall. The latter showed syphilitic arteritis.

G. B. HASSIN.

CHANGES IN THE BRAIN IN LEGAL ELECTROCUTION. GEORGE B. HASSIN, Arch. Neurol. & Psychiat. **30**:1046, 1933.

Organic changes were found in the brains of five criminals executed by electric shocks. The parenchymal changes were: tears, fissuration and cracks of the brain tissue; dislocation, swelling and even liquefaction of the ganglion cells; demyelinization of the white fibers, and an enormous so-called swelling of the oligodendroglia, with dilatation of the shrinkage spaces of His and rupture of the vascular tunics, especially of the elastic membrane. The latter in all the cases was broken up and formed loops, and in some instances the muscularis and the adventitia were also fragmented. Hemorrhages were not present. Another remarkable change was the presence of reactive phenomena (satellitosis and neuronophagia) in the deeper layers of the cortex and in the subarachnoid space (cell proliferation), in spite of the short interval between the action of the electric current and the onset of death. Some changes were similar to those seen in concussion of the central nervous system or in conditions of increased intracranial pressure.

AUTHOR'S ABSTRACT.

THROMBOPHLEBITIS OF THE INFERIOR VENA CAVA AND OCCLUSION OF THE HEPATIC VEINS. R. H. RIGDON, Bull. Johns Hopkins Hosp. **53**:162, 1933.

The literature on endophlebitis hepatica obliterans was reviewed to determine whether such a lesion ever exists in the absence of phlebitis of the hepatic portion of the inferior vena cava. A case is reported in which both lesions were associated.

In the majority of cases of endophlebitis hepatica obliterans reported in the literature the disease was associated with inflammation of the hepatic portion of the inferior vena cava, and there is little support for the opinion that the two processes are different. Furthermore, there appears to be little, if any, justification for the view that endophlebitis hepatica obliterans is a distinct entity.

AUTHOR'S SUMMARY.

CONGENITAL CYSTIC DISEASE OF THE LUNGS. D. H. COLLINS, J. Path. & Bact. **37**:123, 1933.

A case of congenital cystic disease of both lungs is described with a peculiar giant cell hyperplasia of unknown cause in all the lymph nodes.

MASSIVE PARAVERTEBRAL HETEROTOPIA OF MARROW IN A CASE OF ACHOLURIC JAUNDICE. S. J. HARTFALL and M. J. STEWART, J. Path. & Bact. **37**:455, 1933.

A case of massive heterotopia of bone marrow occurring in the thorax of a patient who died of familial acholuric jaundice is reported. The possible relationship of these two conditions is discussed.

AUTHORS' SUMMARY.

THE ISLANDS OF LANGERHANS IN OBESITY. R. F. OGILVIE, J. Path. & Bact. **37**:473, 1933.

A method is described whereby the percentage area of islet tissue in the pancreas and the average area of the islands can be estimated. By this method the islets of Langerhans in nineteen obese patients were compared with those in nineteen lean subjects. Of the obese group thirteen, or 68 per cent, were found to possess (1) an abnormally high percentage area of islet tissue, (2) a normal number of islands per given area and (3) islands the average size of which was definitely greater than the normal. The relationship between the hypertrophied condition of the islets and the obese state is discussed.

AUTHOR'S SUMMARY AND CONCLUSIONS.

STRUCTURAL CHANGES IN ANTIRABIC TREATMENT PARALYSIS. S. GETZOWA, G. STUART and K. S. KRIKORIAN, J. Path. & Bact. **37**:483, 1933.

The predominant feature in two cases of Landry's paralysis following antirabic treatment and in one case of unknown origin was a widespread lesion of ganglion cells inducing rapidly advancing fatal paralysis. The total absence of perivascular zones of demyelinization and perivascular cuffing in the central nervous system argues against the inclusion of antirabic treatment among the somewhat heterogeneous group of factors (smallpox, vaccinia, measles, varicella and typhoid fever) capable of producing acute disseminated encephalomyelitis (Westphal). It also argues against the theory of a virus generally.

MORBID ANATOMY AND HISTOLOGY OF ASBESTOSIS. S. ROODHOUSE GLOYNE, Tubercle **14**:445, 493 and 550, 1933.

The pathologic result of the inhalation of asbestos dust is different from that of the inhalation of other dusts that give rise to diseases, owing to the peculiar long needle-like shape of the particles of asbestos. The fibrosis is diffuse, and nodules such as characterize silicosis are not seen. The various conditions in the asbestos industry render it probable that as time goes on unusual forms of asbestosis will occur. In the pleura the disease is obliterative. In an uncomplicated case the lung shows dense bluish-black areas corresponding to the secondary lobules, surrounded by thick bands of interlobular connective tissue, generally with a reddened background of terminal bronchopneumonia in the less affected portions of the lung. In other organs signs of the disease visible to the naked eye are few.

The affected lung shows particles of five different kinds: (*a*) the carbon pigment common to all dwellers in towns; (*b*) an amorphous brown pigment, presumably blood; (*c*) sharp, jagged particles, probably carbonaceous; (*d*) fibers of asbestos, and (*e*) asbestosis bodies. The fibers of asbestos can also be found readily in the upper respiratory tract. The tissue reaction to the fibers is threefold: (*a*) thickening of the fibers to form asbestosis bodies; (*b*) cellular changes, chiefly accumulation of large phagocytic cells containing the dust and formation of giant cells, and (*c*) fibrosis of the type common to all forms of pneumonoconiosis. The giant cell of asbestosis is a minute collection of phagocytes. The immobilization and long persistence of the phagocytes and especially of the giant cells are characteristic.

The most marked histologic feature of the lung is the holding up of the fibers at the distal ends of the respiratory bronchioles and in the alveolar ducts with the accumulation of large mononuclear phagocytes and the giant cells. In the later stages of the disease, the lymphatics and the adjacent air sacs became filled with asbestos dust and phagocytes. Finally there occurs an increase of connective tissue around the bronchioles, alveolar ducts, air sacs, capillaries and venules, in the interlobular septums and beneath the pleura. These changes ultimately result in complete obliteration of all pulmonary configuration. The disease tends to be most marked in the lower lobes; adherent pleura is almost the rule; the long strand-like or bandlike adhesions seen so frequently in tuberculosis have not been encountered. Pleural effusion is rare. The asbestosis body is a regular concomitant of the disease, but structures closely resembling it are found in other pneumonoconioses. In case of doubt, the golden yellow pigment should be dissolved with strong sulphuric acid. The central fiber of asbestos thus displayed is usually different from the particles seen in pseudo-asbestosis bodies. Tuberculosis and bronchopneumonia are commonly associated with asbestosis, as they are also with silicosis.

H. J. CORPER.

NECROSIS IN THE LIVER FROM POISONING WITH THYROXINE. F. GERLEI, Ann. d'anat. path. **10**:555, 1933.

The toxicity of thyroxine was studied in rabbits. Daily injection of 4 mg. of thyroxine under the skin resulted in the death of the animals within from six to seven days, with extreme emaciation. Central necrosis of the hepatic lobules was found.

AUTHOR'S SUMMARY.

SITE OF FORMATION OF THE SEX HORMONE IN THE HYPOPHYSIS. E. J. KRAUS, Beitr. z. path. Anat. u. z. allg. Path. **91**:245, 1933.

Granting that the hormone which motivates maturation of the ovarian follicle and which is excreted in the urine of pregnant women is produced by the hypophysis, Kraus briefly reviews the evidence favoring the formation of the hormone by one or the other of the three types of cells of the hypophysis. He then presents the results of his histologic study of the hypertrophied hypophyses of seven nonpregnant women with carcinoma of the genital tract and of two women and five men with tumor of the brain. At necropsy urine from the bladder of four of the patients with carcinoma and of three of those with tumor of the brain gave a positive reaction for the hormone by the mouse test. Kraus interprets his findings as indicative of the formation of the hormone by the eosinophilous cells of the anterior lobe. While the mere weight of evidence may be so interpreted, it is to be noted that an individual case may speak just as strongly in favor of formation by one of the other two types of cells. He next presents the results of a series of implantations of bits of the normal and the adenomatous human hypophysis into immature mice. These results, Kraus thinks, indicate that the hormone may be formed by either type of chromophil. Determination of the source of the hormone in pregnancy requires further research.

O. T. SCHULTZ.

MALFORMATIONS OF THE LOWER PART OF THE BODY. E. NACHMANSOHN, Frankfurt. Ztschr. f. Path. **44**:117, 1932.

A stillborn child is described, measuring 36 cm. In place of the lower extremities there was a tail-like structure, 10 cm. in length, taking origin from the pelvic region and becoming gradually smaller to end in a finger-like projection. The external genital organs and the anus were missing. In the region of the lowest portion of the lumbar segment was a small soft projection 1.4 cm. in length, which did not reveal an opening. Only one umbilical artery could be found. No urinary bladder, urachus or persistent cloaca could be made out. The lower portions of the abdominal muscle were markedly hypoplastic. The large intestines were distended and filled with meconium, and the sigmoid colon ended blindly. The surfaces of the serosa were smooth and glistening. Both suprarenal glands were present and normally located, but the kidneys were absent. Close to the umbilical artery two gonads were found, which resembled testes. There was also an occult spina bifida. The explanations for these malformations are given. The author recommends the following classification of malformations of the lower part of the body: (*a*) isolated defects of the external form of the caudal portion of the body, (*b*) isolated defects of the anlagen of the inner organs of the caudal end of the body, and (*c*) isolated defects of the external form of the caudal portion of the body (1) with normally formed and developed inner organs and (2) with defects of the inner organs. This classification does not seem justifiable because (*a*) and (1) overlap.

O. SAPHIR.

SYPHILIS OF THE JOINTS. E. FREUND, Virchows Arch. f. path. Anat. **289**:575, 1933.

This contribution from Erdheim's laboratory is based on the same material that formed the basis of the study of syphilis of bone reported in the preceding volume of *Virchows Archiv* (abstr., ARCH. PATH. **17**:587, 1934). Thirteen syphilitic joints were studied macroscopically, roentgenologically and microscopically; seven were from a single patient, four from another patient, and two from two other patients. In seven instances the involvement of the joint was secondary to perforation by a gumma of the epiphysis into the joint; the perforation usually occurred at the margin of the joint. Fibrous ankylosis was frequent, but cartilaginous union was seen only once. In four instances fractures extended through the weakened bone into the joint. In those instances in which a gumma could not be found either in the epiphysis or in the synovial membrane, the changes in the joint were of the same character as when the arthritis was due to perforation by a gumma into the joint, but were of lesser degree. In no instance was a gumma which had developed originally in the cartilage the cause of syphilitic arthritis. The cartilage of the joint revealed a variety of alterations, which ended sometimes in destruction and sometimes in new formation. Changes similar to those in arthritis deformans, fractures of the bone forming the surfaces of the joints and small hernial outpouchings of the synovial membrane are held to be the results of the syphilitic arthritis.

O. T. SCHULTZ.

GENERALIZED DISEASE OF THE OSSEOUS SYSTEM IN CHILDHOOD. E. HÄSSLER and KRAUSPE, Virchows Arch. f. path. Anat. **290**:193, 1933.

A condition which was clinically diagnosed as aleukemic myelosis in a child, 27 months old, who presented, in addition, osteosclerosis and terminal anemia, is the subject of a comprehensive clinical and roentgenologic report by Hässler. For comparison he includes similar studies of a case of generalized sarcomatosis of the skeleton, with osteolysis and osteoporosis, two cases of osteitis fibrosa cystica and one of Albers-Schönberg's disease, with active rickets, scurvy and anemia. All these conditions occurred in infants. Krauspe follows with a detailed histologic study of the bones in the case of aleukemic myelosis and in that of Albers-Schönberg's disease. He interprets the first condition as primary hyperplastic

disease of the bone marrow, with reactive osteosclerosis, which in turn led to anemia. In the case of Albers-Schönberg's disease both the osseous system and the hematopoietic system were primarily involved. The case of marble disease described had some of the characteristics of von Jaksch's anemia. Krauspe gives also the results of a histologic study of the bones in two cases of lymphatic leukemia and in one case of myeloid leukemia in children. Although osteolytic and osteoporotic changes predominate in leukemia, there may be subperiosteal new formation of sclerotic bone.

O. T. Schultz.

Nodular Lingual Myolysis. A. H. Roffo, Ztschr. f. Krebsforsch. **39**:464, 1933.

Roffo describes a second case of the condition previously termed by him "nodular lingual myolysis." This case occurred in a woman 31 years of age. The lesion was nodular and histologically showed evidence of progressive granulation and disappearance of muscular fibrillae, terminating in complete vacuolar degeneration. The sarcolemma was not affected. There was no involvement of the lymph glands. The only suggestion of an inflammatory reaction was that of a slight hypertrophy of the adjoining mucosa.

H. E. Eggers.

Microbiology and Parasitology

Herpes Encephalitis Problem. F. P. Gay and M. Holden, J. Infect. Dis. **53**:287, 1933.

Additional evidence for the theory that epidemic encephalitis is due to a neurotropic strain of the virus of herpes simplex operative under peculiar conditions of susceptibility on the part of the patient is reported.

From Authors' Summary.

Experimental Pertussis. H. MacDonald and E. J. MacDonald, J. Infect. Dis. **53**:328, 1933.

A filter-passing virus plays no rôle in the etiology of pertussis. The disease is caused by the bacillus of Bordet and Gengou. Active immunity is conferred by the injection of Bacillus pertussis vaccine. [The basis for this summary is experiment on human volunteers.]

Authors' Summary.

Relapsing Fever in California. G. E. Coleman, J. Infect. Dis. **53**:337, 1933.

Relapsing fever caused by three strains of spirochetes isolated in California has been studied in mice, and the disease has been found to be more severe than that caused by S. novyi and possibly than that produced by S. duttoni. Occasionally symptoms attributable to nerve lesions have been observed. The clinical course of an accidental infection in a laboratory worker is described. The exact locality in California where the infective organism in the case originated is uncertain. The blood of two adult guinea-pigs taken on the twenty-second and twenty-third days, respectively, after inoculation infected mice. Although the blood of the guinea-pigs was examined daily, no spirochetes were ever seen. The serum of the animals at this time showed no protective properties against infection in mice. With the California strains, in the absence of spontaneous agglutination, little if any difference in virulence was shown between blood taken during the primary attack and that taken during the first three relapses.

Author's Summary.

Bacteria in the Filtrable State in Bacteriophage. A. I. Kendall and A. W. Walker, J. Infect. Dis. **53**:355, 1933.

Bacteriophage causes bacteria to disappear. Viable bacteria in the filtrable state are present in the filtrates of the phaged bacteria. These bacteria in the

filtrable state are invisible, unstainable and uncultivable by ordinary methods. Hitherto bacteria in the filtrable state have not been demonstrated consistently in filtered phage solutions. This is due presumably in part to difficulties in curbing the action of the phage and partly to circumstances attending the return of these bacteria in the filtrable state to the visible, stainable, nonfiltrable state in which they grow readily in ordinary mediums. Certain procedures are described which by curbing the action of the phage permit these invisible bacteria in the filtrable state to redevelop into nonfiltrable organisms. The methods employed for this purpose were: exposure to methylthionine chloride and sunlight; the addition of living homologous organisms, filtration and the subsequent recovery of the bacteria in the nonfiltrable state from the filtered clear phage solution; the addition of phage to K medium; the addition of killed cultures of the homologous organism; contact with specific antiphage; the use of bile. These procedures, admittedly far from ideal, have, in spite of their obvious imperfection, yielded positive results.

AUTHORS' SUMMARY.

NORMAL FLORA OF PREPUBERTAL VAGINA. H. PETTIT and C. H. HITCHCOCK, J. Infect. Dis. **53**:372, 1933.

Studies of the prepubertal vagina in sixty girls, most of whom were orthopedic patients, show that the flora is predominantly diphtheroid in character. Gram-positive cocci, such as nonhemolytic streptococci and nonpigment-forming staphylococci, are present less frequently and in smaller numbers. Organisms of the intestinal flora seldom if ever occur in healthy children, though in severely ill patients there is a distinct tendency for them, together with Streptococcus aureus, to overgrow the normally occurring flora.

AUTHORS' SUMMARY.

EFFECTS OF COLLOIDAL SILICA ON EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS. S. L. CUMMINS and C. WEATHERALL, J. Hyg. **33**:295, 1933.

The experiments reported confirm the observation by Gye and Kettle that the addition of silica sol to tubercle bacilli leads, on inoculation into guinea-pigs, to a marked increase of local reaction and to a greater local pullulation of tubercle bacilli within the first few days after injection. While a shortening of the survival period was observed in the animals given tubercle bacilli along with silica sol as compared with the guinea-pigs infected with tubercle bacilli alone, the difference was slight and hardly to be regarded as significant. The adjuvant action of the silica sol seems to be local and transitory, as is the local irritant action of silica sol alone; and any tendency to a more rapid dissemination of bacilli appears to be neutralized by the local fibrosis which undoubtedly follows the introduction of silica sol into the tissues. These findings are of interest because they fall into line with the known fact that the tuberculosis death rate in industries involving exposure to silica dust is high in late middle age and after many years of dust inhalation, not in the early years of exposure as should be the case if the silica determined an early generalization of tuberculous infection.

AUTHORS' SUMMARY.

STATISTICS OF ERYSIPELAS IN ENGLAND AND WALES. W. T. RUSSELL, J. Hyg. **33**:421, 1933.

The annual number of notified cases of erysipelas is approximately 17,000, and assuming complete notification of the disease the fatality rate in the cases is approximately 6 per cent. The death rate in terms of the population varies according to age, being highest at the beginning and the end of life and minimal between the ages of 5 and 10 years. The mortality of males is identical with that of females up to the age 25, but is afterward in excess. The disease has in recent years a well marked seasonal incidence—a winter and spring excess with a summer decrease. In this respect it resembles scarlet and puerperal fevers. Although

its seasonal incidence has changed in the course of time, the alteration has not been nearly so pronounced as that of scarlet fever. The incidence is highly correlated with overcrowded conditions. . . . The morbidity from erysipelas is fairly well correlated in time with that from scarlet fever and erysipelas, but in London and other urban districts and in the rural districts of England and Wales the special correlation is very small. Coefficient figures are given.

FROM AUTHOR'S SUMMARY.

ANAEROBIC METHODS FOR THE IDENTIFICATION OF HAEMOLYTIC STREPTOCOCCI. R. M. FRY, J. Path. & Bact. **37**:337, 1933.

This article emphasizes the value of anaerobic cultures in routine efforts to isolate hemolytic streptococci.

THE SIZE OF THE VIRUS OF LOUPING-ILL OF SHEEP. W. J. ELFORD and I. A. GALLOWAY, J. Path. & Bact. **37**:381, 1933.

The size of the virus of louping-ill has been estimated to be from 15 to 20 microns by filtration through carefully graded collodion membranes. The filtration end-point has been checked by inoculation of both mice and sheep. Filtrates infective for mice also proved to be infective for sheep. The virus was found to have retained its infectivity for sheep after twenty-two passages in mice over a period of two hundred and ten days, and also after forty passages in mice extending over a period of six hundred and eighty-seven days. The virus quickly becomes inactivated when kept in broth at a room temperature of from 18 to 20 C. A suspension at p_H 7.6, initially infective in 1:100,000 dilution, had dropped 90 per cent in potency after twenty-four hours and was completely noninfective after three days. The virus may be stored satisfactorily for much longer periods at 4 C. Filtrates of broth suspensions at p_H 7.6 and p_H 8.5, kept in small flasks closed with cotton-wool plugs, were found to be infective after seventy days. The virus exhibits greater stability in slightly alkaline broth, namely at p_H 7.5 to 8.5. Infection has been successfully transmitted to mice with filtrates by a technic of intranasal instillation.

AUTHORS' SUMMARY.

THE GROWTH PHASES OF PLEUROPNEUMONIA AND AGALACTIA ON LIQUID AND SOLID MEDIUM. J. C. G. LEDINGHAM, J. Path. & Bact. **37**:393, 1933.

The morphology and growth phases of organisms isolated in cases of pleuropneumonias and agalactia have been studied in liquid and solid mediums, and the conclusion has been reached that these organisms may be placed, provisionally, in the family Actinomycetaceae. The question of the appropriate genus is reserved for further consideration.

AUTHOR'S SUMMARY.

ACID-FAST ORGANISMS OTHER THAN MAMMALIAN TUBERCLE BACILLI FROM DISEASE IN MAN. AVIAN TUBERCLE BACILLI. ARNOLD BRANCH, Tubercle **14**:337, 1933.

There are a number of authentic cases on record of acid-fast bacilli not mammalian tubercle bacilli infecting man. Some of these strains appear to belong to the avian group while others do not belong to any type of tubercle bacilli, but are probably new strains of pathogenic acid-fast bacteria. Particular difficulty is encountered in diagnosing infection with strains of avirulent avian tubercle bacilli, and a scheme is outlined by which these may be recognized. Avirulent avian tubercle bacilli are capable of forming tuberculin and of sensitizing fowls to a known tuberculin. Inoculation of the common white mouse has proved a useful aid in diagnosing infection with acid-fast strains which are not typical tubercle bacilli or saprophytes. After large intraperitoneal doses multiple abscesses develop in the kidneys.

H. J. CORPER.

PATHOLOGIC CHANGES IN LEUKOCYTES IN TUBERCULOSIS. M. REALE, Beitr. z. Klin. d. Tuberk. **82**:180, 1933.

Changes in the leukocytic blood picture in tuberculosis are usually most striking in acute exudative exacerbations. They do not, however, parallel either the anatomic extent of the process or its immunobiologic type. In general, the variations in the total white cell picture are a more delicate index of the evolution of the disease than are the alterations in the polymorphonuclear cells.

AARON EDWIN MARGULIS.

METABOLISM OF WATER AND CHLORIDES IN TUBERCULOSIS. WILHELM GRÜNEWALD, Beitr. z. Klin. d. Tuberk. **82**:189, 1933.

These investigations were stimulated by the lack of a theoretical basis for the salt-free diets of Gerson and of Sauerbruch and Hermannsdorfer. Grünewald determined the water and chloride content of the lymph nodes, kidneys, suprarenal glands, pancreas, spleen, liver, lungs, heart muscle, bones, skin and striated muscles for normal and tuberculous persons. In general, the organs of the latter contained somewhat more water and definitely less chlorides than the normal controls. It is pointed out that such changes are characteristic of all wasting diseases. The conclusion is therefore reached that salt-free diets are not therapeutically rational in tuberculosis.

AARON EDWIN MARGULIS.

METABOLISM OF TUBERCLE BACILLI. L. M. MODEL, J. P. GURJEFF and A. M. PIROGOFF, Beitr. z. Klin. d. Tuberk. **82**:474, 1933.

The authors studied the biochemical changes occurring in a synthetic medium during the growth and autolysis of tubercle bacilli. The following determinations were made: 1. Glycerin and dextrose are energetically destroyed. 2. No protein-split products are formed until, following exhaustion of all assimilable nitrogen, the growth phase ceases and autolysis sets in. 3. The p_H of the medium decreases during the growth phase but with increasing age of the culture and increasing autolysis rises again, yielding a very typical curve which may be easily differentiated from that given by cultures of paratubercle bacilli, which are invariably alkaline by the end of the six weeks—a difference which may be used diagnostically. 4. Tubercle bacilli can grow under anaerobic conditions. 5. Tuberculin is probably an endotoxin and decreases surface tension.

AARON EDWIN MARGULIS.

SCARLET FEVER WITH PRIMARY INVOLVEMENT OF THE LUNG. HELENE SAWRIMOWITSCH, Beitr. z. path. Anat. u. z. allg. Path. **91**:225, 1933.

Although the earliest localization of the disease process in scarlet fever is usually in the pharynx and tonsils, cases in which the primary lesion is in the skin are not unknown, and a few have been reported in which it was in the larynx or the trachea. The author presents three cases in which the diagnosis of scarlatina could not be questioned and in which there was no involvement of the upper air passages except hyperemia of the pharynx. The primary localization was in the lungs, resulting in a necrotizing lobular pneumonia, in which there were many streptococci and relatively few leukocytes. Each lobular area was surrounded by a zone of fibrinous pneumonia and edema. The character of the inflammatory process is held to be identical with that which occurs in the tonsils in the usual case of scarlet fever. Death occurred early, on the second, fifth and seventh days.

O. T. SCHULTZ.

HISTOLOGY OF TUBERCULOSIS OF BONE. A. N. TSCHISTOWITSCH and S. WINOGRADOW, Beitr. z. path. Anat. u. z. allg. Path. **91**:236, 1933.

In twelve cases of miliary tuberculosis of children and adults the marrow of the diaphysis and epiphyses of the femur and that of the sternum were examined

histologically for the purpose of determining the character of the earliest lesion in tuberculosis of bone. The earliest lesion was a miliary granuloma with a prominent fibrillated reticulum. Necrosis occurred first at the center of the granuloma, and not in the otherwise unchanged marrow as has been asserted by some. Destruction of osseous trabeculae was secondary to necrosis of the granulomas.

O. T. SCHULTZ.

ETIOLOGY OF APPENDICITIS. M. GUNDEL, W. PAGEL and F. SÜSSBRICH, Beitr. z. path. Anat. u. z. allg. Path. **91**:399, 1933.

This thorough study of the bacterial etiology of appendicitis is based on thirty-one cases of acute appendicitis, thirty of acute appendicitis with perforation and peritonitis, seventeen of appendical abscess, fifty of chronic appendicitis and seventeen appendixes of the kind that are referred to in the German literature as "stolen appendixes." The work consisted in a bacterioscopic and cultural examination of material from three places in the lumen of the appendix and of material from the throat, a histologic examination of the appendix, with especial reference to the localization of bacteria, a cultural study of the blood just before or after operation, and a bacteriologic study of the stool. The authors conclude that acute appendicitis is an infection by autogenous enterogenous bacteria. The most common causative agent is the enterococcus or the closely related anhemolytic streptococcus. There was no constant or even suggestive relationship between the flora of the appendix and that of the throat. In three cases, however, the same type of pneumococcus was isolated from the appendix as from the throat. A bacterial relationship between acute appendicitis and acute angina is denied. Although the enterococcus is the most important cause of acute appendicitis, in appendical abscess and in peritonitis following perforation the colon bacillus is the most important organism. In these two complications the gas bacillus was also frequently encountered but is believed to have had little part in the inflammatory process. Blood cultures were negative, with the exception of one case in which the colon bacillus was isolated.

O. T. SCHULTZ.

EOSINOPHIL REACTION IN ACTIVE TUBERCULOSIS. F. A. MICHAILOW, Virchows Arch. f. path. Anat. **289**:315, 1933.

A decrease in the number of eosinophilic leukocytes in the peripheral blood after the injection of a minute quantity of tuberculin is of diagnostic value in determining the activity or the quiescence of tuberculosis in adults. The quantity of tuberculin must be so small that it will not cause a nonspecific reaction. The eosinophilic cells of blood diluted with Dunger's eosin-acetone mixture are counted in the hemacytometer. Then 0.1 cc. of a 1 : 100,000,000 dilution of Denys' tuberculin or of a like dilution of Koch's old tuberculin is injected beneath the skin of the shoulder. Thirty minutes after the injection the eosinophilic leukocytes are counted again. A decrease of 5 per cent is considered to show a positive reaction. The reaction is negative, i. e., the number of eosinophils is increased or remains unchanged in persons with inactive tuberculosis, in healthy persons and in those ill of diseases other than tuberculosis. The reaction is positive in adult persons with active tuberculosis and in tuberculous children, and has diagnostic value in differentiating between active tuberculosis and other infections. The reaction is of no value in cases of advanced tuberculosis, in those in which tuberculin is being or has been administered therapeutically, and in those in which the intial eosinophil count is low. The reaction is ascribed to the protein fraction of the tuberculin. In echinococcus disease the injection of minute quantities of echinococcus liquid yields a similar diagnostic reaction.

O. T. SCHULTZ.

REACTIVE RETICULO-ENDOTHELIOSIS. V. UHER, Virchows Arch. f. path. Anat. **289**:504, 1933.

A child, aged 21 months, died of streptococcic sepsis seventeen days after the onset of the illness with acute angina. Fourteen days before death the leukocyte

count was 11,000, with 22 per cent lymphocytes and 3 per cent monocytes. The reticulo-endothelial system of the spleen, lungs, lymph nodes and intestine at necropsy was in a state of reactive hyperplasia. The liver and bone marrow took very little part in the reactive process.

O. T. SCHULTZ.

EXTRAPHARYNGEAL SCARLET FEVER. A. M. TROIZKAJA-ANDREEWA, Virchows Arch. f. path. Anat. **289**:718, 1933.

Cases of scarlet fever in which the primary localization is in a part of the body other than the pharynx and tonsils have been long known and frequently described as surgical, puerperal and wound scarlet fever. According to the author, histologic study of the primary focus is wanting in most such cases. He therefore presents a detailed histologic study of the local lesion in six of sixteen patients with extrapharyngeal scarlet fever who died in a hospital for infectious diseases of children in Leningrad. In eight of the patients a clinically typical attack of scarlet fever followed burns of the skin. In the remainder the point of entrance was a cutaneous eruption or a slight injury of the skin that became infected. The local lesion was characterized by widespread necrosis and purulent infiltration of the skin and underlying fat. Streptococci were numerous in the inflamed tissues. The regional lymph nodes revealed necrosis and the presence of fibrinous exudate in the sinuses. That extrapharyngeal scarlet fever is true scarlet fever must be determined by clinical and epidemiologic considerations. It differs from true scarlatina in no way except that the period of incubation may be shorter and the mortality higher. That a case of scarlet fever is extrapharyngeal in origin must be determined by the absence of acute inflammatory reaction in the tonsils and cervical lymph nodes and by the presence of a necrotizing, purulent process elsewhere.

O. T. SCHULTZ.

INFLUENCE OF SOME END-PRODUCTS OF METABOLISM ON EXPERIMENTAL TUBERCULOSIS OF GUINEA-PIGS. PIETRO RONDONI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **77**:264, 1932.

Young animals (from 200 to 300 Gm.) were infected with tubercle bacilli of rather low virulence and given repeated injections of small doses of uric acid, creatine or histamine. Uric acid had an aggravating influence and creatine a slightly inhibitory effect on the tuberculous infection. The infection was not influenced by the injections of histamine, but, on the other hand, susceptibility to histamine seemed elevated in the tuberculous animals.

I. DAVIDSOHN.

Immunology

EXPERIMENTAL RESEARCH ON YELLOW FEVER. J. LAIGRET, Arch. Inst. Pasteur de Tunis **21**:412, 1933.

In a second series of seven persons vaccinated with the mouse virus of yellow fever, fever developed in three. In one only a febrile reaction occurred; the other two presented various symptoms. Although efforts to recover the virus were unsuccessful, it was believed that the mouse virus, which was not fixed, was not sufficiently attenuated to induce a desired completely silent infection. Attenuation similar to that secured by drying the virus of rabies was accomplished by holding the virus at between 10 and 20 C. Two preparations, one a suspension of glycerin held at ordinary temperature and the other a dried material, failed to kill mice, but induced the formation of protective substances. They had not been tried on man.

FROM THE AUTHOR'S CONCLUSIONS.

HEMOLYSIS: I-V, HECTOR DIACONO, Arch. Inst. Pasteur de Tunis **21**:557, 579 and 594, 1933; **22**:47 and 212, 1933.

In a series of articles a complete review of the subject of hemolysis is presented, including original research. The first article deals with hemolysis resulting

from distilled water and from other physical factors. The second is concerned with the action of organic and inorganic chemical agents of many types. In the third various bacterial agents are considered, as well as toxins and venoms of vegetable and animal origin. The following study takes up all phases of hemolysis resulting from the use of lytic antibodies and complement. In a fifth article original studies are presented, dealing chiefly with the various factors, physical, chemical, metabolic, etc., affecting the production of antibodies and the mechanism of reaction. The series is concisely presented, although it forms the equivalent of a monograph of 255 pages.

M. S. MARSHALL.

BLOOD GROUP FERMENT AND ELIMINATION OF BLOOD GROUP SUBSTANCE. E. WITEBSKY and T. SATOH, Klin. Wchnschr. **12**:948, 1933.

The stools of adults do not show any group-specific reactions. However, meconium and the stools of the new-born are rich in group A, which disappears during the course of the first year. Schiff believes that this deficiency of group characteristics in the adult is due to the presence of a special blood group ferment. Witebsky and Satoh obtained a Berkefeld filtrate of stool extract and demonstrated that it has a destructive action on group A in saliva. This blood group ferment develops in the stool during the course of the first year.

JACOB KLEIN.

THE DIAGNOSIS OF LEPROSY BY THE REACTION OF WITEBSKY. YOSHIO AOKI and KITOSHI MURAO, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:365, 1933.

Witebsky, Klingenstein and Kuhn prepared a highly sensitive antigen from tubercle bacilli. It reacts with serums of tuberculous patients and, according to Brants, also with serums of lepers. Aoki and Murao checked the results of Brants on serums of thirty lepers and found the original antigen of Witebsky highly sensitive. They also prepared an antigen from lepromas according to the directions given by Witebsky for the preparation of the antigen from tubercle bacilli. The antigen from leproma was less sensitive and less specific than that from tubercle bacilli.

I. DAVIDSOHN.

CHEMICAL NATURE OF ANTIGENS EMPLOYED IN THE DIAGNOSIS OF SYPHILIS. E. BALBI, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:372, 1933.

Ö. Fischer showed that when an alcoholic extract of beef heart is treated with aluminum hydroxide it loses its ability to fix complement in the presence of syphilitic serums. The reacting substance could be recovered from the adsorbent by washing it with benzene, and the latter reacted as well as the original extract. Balbi confirmed the results of other authors concerning the antigenic qualities of alcoholic extracts of beef heart when injected into rabbits and the failure of extracts which were adsorbed with aluminum hydroxide to produce lipoid antibodies in the animal. In addition, Balbi reports the production of complement-fixing antibodies following injection into rabbits of benzene washings of aluminum hydroxide, with which an alcoholic extract of beef heart was adsorbed. The immune serum reacted with the native extract and with the benzene washings but not with the adsorbed extract. The results indicate a far reaching parallelism of reactions in vivo and in vitro.

I. DAVIDSOHN.

THE M AND N COMPONENTS. GUENTER BLAUROCK, Ztschr. f. Immunitätsforsch u. exper. Therap. **79**:377, 1933.

The article begins with a review of publications on the inheritance of the qualities M and N. Seven hundred and fifty-four families with 2,179 children have been studied (559 families and 1,251 children in Europe and the rest in the United States). All the reports, including Blaurock's study of 80 families, confirm

the original assumption of Landsteiner and Levine that the qualities M and N are inherited as a simple mendelian pair of two allelomorphic genotypes. The few (8) exceptions can well be attributed to illegitimacy. Blaurock advocates the recognition of these two qualities for medicolegal purposes. He recommends the absorption of anti-N immune serums for purposes of purification at room temperature in addition to the absorption in the incubator. A technic of agglutination on thick concave slides is described.

I. DAVIDSOHN.

THE CHEMICAL NATURE OF ANTIGENS EMPLOYED IN THE DIAGNOSIS OF SYPHILIS: III. Ö. FISCHER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:391, 1933.

Fischer reports additional studies on the nature of the chemical changes occurring when the reacting substance of the alcoholic extract of beef heart is removed by means of aluminum hydroxide and when it is then again liberated by washing the aluminum in benzene. The washings contain more fatty acids and particularly more reducing substances and less phosphatide and nitrogen than the original extract.

I. DAVIDSOHN.

THE MECHANISM OF THE URTICARIAL IDIOSYNCRASY TO EGG WHITE IN THE ECZEMATOUS CHILD. WERNER JADASSOHN and FRITZ SCHAAF, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:407, 1933.

Dialysates of egg white are known to be urticariogenic in the allergic eczematous child. Opinions differ as to whether the reacting substance is of protein nature, or, as Jadassohn and Schaaf and others maintain, a nonprotein substance. When the proper technic is employed, no protein substances pass into the dialysate. An analysis of the reports to the contrary discloses faults in the technic of dialyzing or in the methods of determining the presence of protein substances in the dialysates. The comparison, by means of the Prausnitz-Küstner technic, of the urticariogenic potency of egg white and of dialysate revealed that the latter reacted in quantities which could not contain the minimum concentration of protein found necessary in quantitative tests with egg white. By means of the Prausnitz-Küstner technic it was possible to demonstrate that chicken egg white contains at least two antigenic substances; one of them is also present in duck egg white. Both pass through the dialyzing membrane. The blood serum of eczematous children with urticarial hypersensitiveness to egg white contains substances which can neutralize the urticariogenic properties of egg white. By means of the Schultz-Dale technic trichophytin produced anaphylactic phenomena in dilutions which made it probable that that reaction was not due to protein substances. Jadassohn and Schaaf conclude that urticarial hypersensitiveness and anaphylaxis are closely related.

I. DAVIDSOHN.

THE DIAGNOSIS OF WEIL'S DISEASE WITH COMPLEMENT FIXATION AND PRECIPITATION. W. GAEHTGENS, Ztschr. f. Immunitätsforsch. u. exper. Therap. **79**:428, 1933.

The antigen was prepared from cultures of Spirochaeta icterogenes on Uhlenhuth's or Korthof's mediums. Cultures of proper density were washed and suspended in phenolized physiologic solution of sodium chloride. The complement-fixation test gave results comparable with those of the older agglutination test, but only in about three to four times stronger dilutions of the serum. The methods complement each other. Precipitation tests based on the use of the benzochol extract of Sachs and his associates and on the clearing reaction of Meinicke gave results similar to those of the two previously described procedures but were unfit for differentiation of Weil's disease from syphilis.

I. DAVIDSOHN.

THE ANAPHYLACTIC SHOCK AS "MODEL" EXPERIMENT FOR ALLERGIC DISEASES. P. MANTEUFEL and R. PREUNER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:65, 1933.

The use of animals for the study of the therapy and prophylaxis of human allergy lacked comparative value when intravenous or intracardiac injections were necessary for the production of the anaphylactic shock. On the other hand, the Arthus phenomenon was not sufficiently sensitive. Manteufel and Preuner confirmed the results of previous authors who introduced the inhalation experiment. It permits the reproduction of anaphylactic reactions which resemble the disease in man both in the circumstances under which it occurs and in the symptoms. There is no need for repeated experiments to determine the active dose, and the same animal can be employed repeatedly.

I. DAVIDSOHN.

INFLUENCE OF CONCENTRATION ON COMPLEMENT-FIXATION. EDITH SUSSMANOWITZ, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:95, 1933.

The fixation of complement by protein antiserums was directly proportionate to the concentration of the complement and inversely proportionate to the volume of the complement dilution, (the volume of antigen and of antiserums remaining unchanged). That effect was evident only during the phase of complement fixation (primary incubation). Subsequent addition of physiologic solution of sodium chloride did not affect the intensity of the complement fixation. The effect of the concentration was particularly noticeable when secondary incubation was prolonged, indicating that also the stability of the complement was increased in higher concentrations. When the period of the primary incubation was shortened, the difference was marked also after a short period of secondary incubation. The specificity of the reaction was not affected by the concentration of the complement. The intensity of the complement fixation was further increased by lowering the concentration of the sodium chloride during the period of primary incubation and by decreasing the quantities of the antiserum. A similar but much less marked increase in the intensity of the reaction was observed with antibacterial immune serum, but when lipoid antiserums were employed, the concentration of the complement and the total volume did not affect the intensity of the complement fixation.

I. DAVIDSOHN.

THE SEROLOGIC SPECIFICITY OF SALIVA. ERNST WITEBSKY and WERNER HENLE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:108, 1933.

Immune serums produced in rabbits treated with centrifugated and inactivated saliva reacted specifically with their homologous antigen in the complement-fixation test. There was some rather irregular reaction also with human serum. Some antiserums produced by injection of human serum did not react with saliva in the complement-fixation test. The specific salivary substance was highly thermoresistant. The enzyme which destroys the group-specific substance of the saliva acts similarly though not quite as regularly on the salivary specific substance.

I. DAVIDSOHN.

GROUP-SPECIFIC DIFFERENTIATION OF THE BLOOD OF HORSES. S. SCHERMER and A. KAEMPFFER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:146, 1933.

By proper experiments on cross-absorption, six group-specific qualities in the red blood cells and six corresponding iso-agglutinins in the serum were established. The A α shows a differentiation similar to that existing in man: a highly sensitive A (A_1) and a weakly sensitive A_2; a strong α and a weak α. The α_1 may coexist with A_2 in the same horse without an interaction. Such a combination is physiologic. There is no qualitative difference between the two A qualities. The four new pairs of agglutinable and agglutinating qualities are X-x, Y-y, Z-z and V-v. The V-v pair is characterized by a very low titer. The finding of the new

qualities makes it possible to classify the blood of horses without the acceptance of hypothetic subgroups. Schermer and Kaempffer emphasize that they employ the terms A and B as indicating in the horse properties similar to but not necessarily identical with the corresponding human qualities.

I. DAVIDSOHN.

THE ELIMINATION OF GROUP AND SALIVA SPECIFIC SUBSTANCES. WERNER HENLE, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:171, 1933.

Henle confirms the observation of Schiff and Sasaki that human beings can be divided into two groups: those who eliminate their group-specific qualities in the saliva, and those who do not. There is no relation between the ability to eliminate these substances and the presence in the saliva of ferments which are known to destroy the blood group qualities. The specific antigenic salivary substance and the species-specific quality are found in the saliva of the eliminators of the group-specific qualities as well as in that of the noneliminators. The existence of a specific quality "O" in the saliva, as maintained by Schiff, is questioned. It may be mimicked by a demonstrated nonspecific action of concentrated saliva.

I. DAVIDSOHN.

BLOOD GROUPS IN THE INSANE. I. SOMOGYI and L. ANGYAL, Orvosi hetil. **76**:265, 1932.

A comparison of the percentage distribution of the blood groups of 608 male and 392 female patients with psychoses with the results of the investigations of Verzar and Weszeczky on the distribution of these groups among healthy Hungarians gave the following results: 1. There are no essential differences between the distributions of the blood groups in the healthy and the insane population. 2. There is no characteristic distribution for the different types of psychoses. 3. Persons with nervous and psychotic diseases of syphilitic origin show the same distribution of blood groups as the healthy population. 4. Identity or differences of blood groups do not influence the time of incubation or the type of fever in patients inoculated with malaria. 5. Malarial treatment does not result in any alteration of the groups. 6. No correlation is found between psychopathic heredity and the transmission of blood groups.

WILLIAM FREEMAN.

Tumors

A NEW TRANSPLANTABLE TUMOR OF THE RAT. D. P. SECOF, Am. J. Cancer **19**:1, 1933.

The tumor appeared in the supra-orbital region. It has been transplanted through nineteen generations, about 30 per cent of the transplants taking. It grows best in the peritoneal cavity. In structure the tumor resembles a carcinoma, but the type cell suggests that it may belong in the endothelioma or myeloma group. No differentiation in structure has taken place during transplantation. This paper records data on transmission and structure.

EXTRAGENITAL CHORIONCARCINOMA IN THE MALE. H. G. HEANEY, Am. J. Cancer **19**:22, 1933.

A review of the literature disclosed reports of 131 cases of chorioncarcenoma in males. In more than 90 per cent the growth arose primarily in the testicle. In some cases the origin was doubtful, but in at least 7 it seems to have been definitely extragenital and to this group Heaney adds an eighth case. This was a tumor of choriocarcinomatous structure arising in the retroperitoneal tissue of a man 40 years of age. Of the numerous theories of the histogenesis, that assigning the origin to the urogenital anlage appears to be the most satisfactory explanation in this case.

FROM THE AUTHOR'S SUMMARY.

MULTIPLE HEMANGIOMAS IN AN INFANT. A. C. TAYLOR and E. MOORE, Am. J. Cancer **19**:31, 1933.

In an infant multiple hemangioma involved the skin, liver and lungs. The question of metastasis is discussed, but no definite conclusions are reached.

THE ABDERHALDEN REACTION IN THE DIAGNOSIS OF MALIGNANT TUMORS. M. SANCHEZ, Am. J. Cancer **19**:40, 1933.

Employing nine substrata, Sanchez made 228 Abderhalden tests, with definite results in 185. The most clearcut reactions were obtained with substrata prepared from a carcinoma of the stomach and a sarcoma of the uterus. With a mixture of these two tumors (substratum D) 152 definite reactions were obtained in 127 tests, with a percentage of error of 8.6. Including the uncertain readings and the tests without result, the percentage of error was 23.7. The failures include those due to defects of apparatus as well as those due to the character of the material tested. FROM THE AUTHOR'S SUMMARY.

KERATINIZING EMBRYONAL NEPHROMA OF THE KIDNEYS OF THE CHICKEN. W. F. FELDMAN and C. OLSON JR., Am. J. Cancer **19**:47, 1933.

Bilateral embryonal renal tumors were observed in a cross-bred cockerel, 10 months of age. The right kidney was practically obliterated by a tumor that weighed approximately 100 Gm. The tumor of the left kidney was much smaller and was confined to the region just under the ureter. Metastasis had not occurred. Microscopically these tumors disclosed a variety of cellular elements characteristic of a nephrogenic form of neoplasm of the fetal type. Adenomatous structures were common, and the cells of many of these were undergoing keratinization, with the formation of numerous cornified nodules or epithelial pearls. In the larger tumor cornification was the most prominent feature. AUTHORS' SUMMARY.

CARCINOMA OF THE SKIN IN CHILDHOOD. JAMES R. LISA, Am. J. Dis. Child. **46**:561, 1933.

A boy, 10 years of age, of Polish parentage, had a pedunculated mass on the left side of the lower lip occurring below the mucocutaneous border. It had first been noted about six months previously as a pinhead-sized, cherry-red, hard growth, and it had gradually grown to the size of a pea. Microscopically the tumor was covered by thin squamous epithelium. The rete pegs displayed a marked tendency toward downward growth and branching. At the tips of the pegs the epithelial cells were large and irregular in size and shape; they displayed hyperchromatic nuclei, and the basement membrane was absent. Between the pegs the epithelium was normal. Throughout the dense fibrous subcutaneous tumor mass were scattered, individually and in nests, cells of the same character as those at the tips of the pegs, showing an extreme degree of anaplasia. Within many of the lymphatic channels were masses of very large anaplastic cells. Mitoses were infrequent. The patient has apparently remained free from recurrence or metastasis for one year but is still under observation. RALPH FULLER.

GRANULOMA CELL HYPERPLASIA OF THE OVARY. J. I. BREWER and A. O. JONES, Am. J. Obst. & Gynec. **25**:505, 1933.

Three cases of ovarian tumor due to granulosa cell hyperplasia are described. In all three the growth was associated with uterine bleeding, although two of the cases occurred after the menopause. Metastases were not found, nor have recurrences been observed. It is concluded that growth of this type is not a tumor, but rather hyperplasia of the granulosa cells, which have their origin in embryologic rests of the germinal epithelium. The growth is probably benign, and produces a hormone that is the cause of the uterine bleeding. JACOB KLEIN.

THE INFECTIVE AGENT IN TUMOUR FILTRATES: A FURTHER INVESTIGATION BY MEANS OF ANTISERA TO NORMAL TISSUES. W. E. GYE and W. J. PURDY, Brit. J. Exper. Path. **14**:250, 1933.

In 1931 we published evidence that when a Fujinami tumor passes from fowl to duck something essential to infectivity changes, since filtrates can no longer be neutralized by immune serum prepared in goats by means of minced fowl embryo. In the first part of the present paper the reverse process is directly demonstrated by means of serum taken from a goat immunized with minced duck embryo. In the later parts of the present paper it is shown that serum taken from a goat immunized by means of fowl red cells will neutralize extract of fowl-grown Fujinami tumor. It is shown also that this same immune serum does not affect the potency of extract of duck-grown Fujinami tumor. Serum prepared in a goat by means of fowl plasma is shown not to affect the potency of filtrate prepared from Fujinami tumor, whether fowl or duck; and the same is shown to be true of serum prepared by means of duck plasma. AUTHORS' SUMMARY.

THE HETERO-TRANSFER OF TWO FILTERABLE TUMOURS: AN INVESTIGATION BY MEANS OF IMMUNE SERA. W. J. PURDY, Brit. J. Exper. Path. **14**:260, 1933.

A serologic method dependent on the published observations of Gye and Purdy has been used in a reinvestigation of the way in which daughter-tumors are formed when tissue from fowl-grown Rous and Fujinami tumors is injected into ducks. The new method shows that in adult ducks new Fujinami tumors arise solely because cells of the host become infected and multiply. It shows also that in ducklings Rous sarcoma 1 is propagable solely because the tumor cells of the inoculum become established and multiply; no infection of host cells takes place. Thus by an independent method conclusions drawn from observations made on ducklings which had received an injection of embryo tissue have been confirmed. Gye and Purdy (1931) concluded that the species-specific element which is present in an active tumor filtrate and is necessary for infectivity must be derived from the tumor cells themselves, and not from normal tissues of the host. The accuracy of this conclusion is proved by new facts. AUTHOR'S SUMMARY.

ACTIVE IMMUNIZATION OF PHEASANTS AGAINST FOWL TUMOURS. C. H. ANDREWES, J. Path. & Bact. **37**:17, 1933.

Rous sarcoma 1 has been propagated in series through four pheasants, and transplantation could probably have been carried on indefinitely. In addition to the tumors mentioned in an earlier paper, two other fowl tumors (Begg's MH 2 and Baker's BS 1) have been transplanted into pheasants. Pheasants resisting repeated inoculations of tumors to which they are relatively refractory are subsequently found to be immune to filtrates or cells of Rous sarcoma and Fujinami sarcoma. Evidence is given that this immunity depends primarily on immunity to tumor virus antigen; immunity to fowl protein may, however, play a subsidiary rôle. AUTHOR'S SUMMARY.

FURTHER SEROLOGICAL STUDIES ON FOWL-TUMOUR VIRUSES. C. H. ANDREWES, J. Path. & Bact. **37**:27, 1933.

Serums from fowls bearing the fibrosarcomas MH 1 and CT 10 neutralize filtrates of the following tumors: fibrosarcomas MH 1 and RF 11, spindle cell sarcomas RF 4, BS 1 and Rous 1, and endothelioma MH 2. They fail to neutralize the virus of Fujinami's myxosarcoma. On the other hand, ducks recovered from Fujinami tumors and hyperimmunized have serum which will neutralize not only Fujinami virus but also, though less readily, Rous, MH 2, BS 1 and RF 4 viruses. Rous and Fujinami viruses can be shown to be antigenically different from one another. Of the tumor viruses studied, Fujinami's is neutralized only by homo-

logous (anti-Fujinami) serum; Rous 1 is readily inactivated by many heterologous serums; RF 4, RF 11, MH 2 and BS 1 stand in an intermediate position. The few "normal" fowl serums with neutralizing properties have proved active particularly against Rous virus, less so against RF 4, RF 11, MH 2 and BS 1, and not at all against Fujinami virus. The fowl tumor viruses which have been thoroughly studied all have some degree of antigenic relationship, but no two have yet been found to be serologically identical. They are probably interrelated much as are the members of some groups of bacteria. AUTHOR'S SUMMARY.

VITAL STAINING OF THE ROUS SARCOMA. A. HADDOW, J. Path. & Bact. **37**:149, 1933.

By the use of the intravital staining technic it is shown that the tumor appearing after an inoculation of active cell-free filtrates of sarcoma is derived from previously normal cells under the influence of the agent. From the morphology of the cell and its content and distribution of segregated dye it is shown that the unit initially affected is the free histiocyte, and that this must be regarded as the parent cell of the Rous sarcoma. AUTHOR'S SUMMARY.

HISTOLOGIC STUDIES OF CARCINOMA OF THE CERVIX AFTER TREATMENT WITH RADIUM. GOFFREDO FROLA, Arch. internat. de méd. expér. **8**:289, 1933.

Twenty-four hours after the beginning of the treatment with radium typical mitosis ceased; atypical mitosis was considerably diminished also. Pyknotic changes increased markedly for several days. At the end of the treatment there was a modification in the volume, form and color of the nucleolus. The size of the cells gradually increased after treatment, slightly in adenocarcinoma, but considerably in epidermoid carcinoma. The cytoplasm showed cloudy swelling and vacuoles; the nucleus was distorted by pyknosis, swelling, vacuolation or lysis. The connective tissue became more dense, and the inflammatory reaction, which at first may have been predominantly lymphocytic, became plasmocytic and finally leukocytic. The number of eosinophils increased toward the end of the treatment; this may have been due to irritation by lactic acid and was of no particular significance. The blood vessels were practically always affected by radium; there was proliferation of the intima as well as thrombosis; frequently there was fibrinoid degeneration of the media. Resorption of the necrotic tumor occurred by lysis and by the action of microphages and macrophages. This was followed by sclerosis of the connective tissue. Giant cells similar to those around foreign bodies were also seen. The radium caused a hyperplasia of the mucous glands of the cervix. These glands are resistant to radium and frequently undergo anaplasia or metaplasia. Even after preliminary treatment with x-rays, radium does not destroy mitosis (typical and atypical). JACOB KLEIN.

THE PATHOGENESIS OF MYXOMA. T. GRECO, Tumori **7**:134, 1933.

Pure myxoma originates from embryonic tissue. In the myxosarcoma group only the minority can be considered pure malignant myxoma, the majority being sarcoma with a few islands of degenerated mucoid tissue. E. VON HAAM.

CARCINOSARCOMA OF THE PROSTATE GLAND. C. PANA, Tumori **7**:244, 1933.

A man 59 years old had a tumor of the prostate gland showing ths histologic picture of small round cell sarcoma and adenocarcinoma. A metastasis in the lymph glands showed the structure of round cell sarcoma. E. VON HAAM.

CYTOLOGIC STUDIES OF MALIGNANT TUMORS. U. C. BAGOZZI, Tumori **7**:266, 1933.

Golgi's apparatus and the mitochondria were studied in tumor cells of man and animals. It was found that the Golgi apparatus in cells of benign tumors

and tumors of low grade malignancy is similar to that in normal cells, and that it is only in the cells of very atypical and very malignant tumors that the structure is different. The mitochondria were found to be of a typical cytoplasmic formation, and no difference between the structure of normal cells and that of malignant cells could be detected.

E. VON HAAM.

IMPORTANCE OF THE MALIGNANCY INDEX OF HUEPER AND SCHMITZ IN THE TREATMENT OF CARCINOMA OF THE UTERUS. M. STRANI, Tumori **7**:289, 1933.

The following characteristic signs mentioned in the malignancy index of Hueper and Schmitz are of great significance in the prognosis and treatment of carcinoma of the uterus: (1) the type of carcinoma and the degree of maturity or differentiation; (2) the type of the infiltrating growth; (3) the size and the shape of the single cells; (4) the sharp demarcation of the limits of the single cells; (5) the irregularity of the shape and size of the cell nucleus, and (6) the number and especially the atypical appearance of the cell mitoses.

The relationship between the nuclear substance and the plasma, the vascularization of the tumor and the degree of inflammatory reaction are of little value for prognosis and therapy.

E. VON HAAM.

CYLINDROMATOUS TUMOR OF THE PAROTID GLAND. AARNO SNELLMAN, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:11, 1933.

A thorough microscopic study of five cases of so-called parotid cylindroma (adenocarcinoma?) was made with particular attention to the parenchyma and the hyaloid formations in the stroma. The latter structures are thought to be due to a combination of the parenchymal secretions with the stroma, which results in an irreversible reaction.

JACOB KLEIN.

CELL STRUCTURE OF RODENT ULCER. C. THESLEFF, Arb. a. d. path. Inst. d. Univ. Helsingfors **7**:51, 1933.

A microscopic study of forty-eight specimens of rodent ulcer was made. Solid basal cell carcinoma occurred in more than half the cases. Hyaline pearls and concentric cell formations were frequent. In seven instances a metatypical struture was observed in which the cells were rich in plasma and contained radial structures. The stroma was vascular in these specimens. The presence of plasma cells, granulocytes, lymphocytes and mast cells indicated secondary infection. With special silver stains a definite network was demonstrated, as well as nuclear formations. There are included numerous illustrations, as well as a review of important theories explaining the pathogenesis of rodent ulcer.

JACOB KLEIN.

SYMMETRICAL SQUAMOUS CELL CARCINOMA IN SCARS OF BURNS ON THE LEGS. GEORG ARNDT, Beitr. z. klin. Chir. **157**:305, 1933.

Symmetrical bilateral carcinoma of the extremities developing in scars from burns is reported for the first time. The 44 year old woman had large carcinomatous ulcers on both legs, extending from the region of the ankle to the middle of the leg. The burns occurred 41 years previously. Ulceration developed in the scars after she was 26 years of age. The ulcers healed during several pregnancies, but finally increased in size. Both legs were amputated, and the patient was without recurrence one year after operation. Histologically the tumors were ripe squamous cell carcinomas. Ninety-nine instances of cancer in scars from burns have been collected from the literature. The occurrence in men has been three times as frequent as in women. The average age was 47 years. Carcinoma may develop shortly after a burn or after intervals as long as sixty-nine years. Like other

carcinomas of the skin that developing from the scar of a burn is the least malignant form of squamous cell carcinoma and offers a fair prognosis (cures in 62 per cent of the cases).

G. ALEXANDER HELLWIG.

GROWTH OF HUMAN TUMORS IN VITRO. Z. ZAKRZEWSKI and W. KRASZEWSKI, Klin. Wchnschr. **12**:1495, 1933.

Cultures of human tumor tissues were made in Carrel flasks. The solid phase was coagulated chicken plasma washed with Tyrode solution; the liquid phase was diluted human serum with heparin. In cultures of twelve different tumors both tumor and stroma elements grew, the latter cells with greater activity. All of the tumor tissues investigated grew well in cultures for from two to four months. These results oppose the concept of a specific tumor-stimulating substance. As has been stated previously, apart from fundamental contrasts between normal and tumor cells no further qualitative differences can be demonstrated. In spite of unsuccessful inoculation of these tissues in human hosts the tissue cells, in their cultural behavior, are malignant.

E. F. HIRSCH.

ACTIVE COLLOID IN A METASTATIC THYROID CARCINOMA. R. B. ENGELSTAD, Ztschr. f. Krebsforsch. **39**:369, 1933.

A patient, 82 years of age, had had for twenty years a goiter without perceptible evidence of change. There developed a metastatic lesion of the skull cap, histologically evidently a carcinoma of the thyroid gland. Active colloid could be demonstrated in this, in a quantity of over 0.25 mg. per gram.

H. E. EGGERS.

Society Transactions

PATHOLOGICAL SOCIETY OF EASTERN NEW YORK

ARTHUR W. WRIGHT, *Secretary*

Regular Meeting, Oct. 13, 1933

J. SCHLEIFSTEIN, *Presiding*

GENERALIZED METASTATIC MELANOMA. V. W. BERGSTROM.

A married white woman, aged 49, was first taken ill nine weeks before death. She complained of nausea and vomiting as well as an indefinite feeling of distress without pain. There was one fainting spell with unconsciousness four weeks before death. No paralysis or convulsions were noted, but there was slight spasm of the left eyelid and the pupils reacted slowly to light. Moderate edema of the ankles improved with rest in bed. Nervousness and restlessness were marked. The pulse rate averaged about 36 per minute but occasionally went as high as 100; the temperature never went above 100 F.; the respirations did not exceed 26 per minute.

The hepatic dulness reached to the brim of the pelvis. Innumerable bluish-gray, shotlike nodules developed in the skin and mucous membranes over the entire body less than two weeks before death. The nails and conjunctivae were not involved however. Examination of an excised nodule showed it to be a melanoma. No pigmented warts or moles could be found, although there were a few simple non-inflamed warts on the back. There was likewise no evidence of tumor in the eyes. The urine contained a small amount of albumin and a moderate number of granular and hyaline casts. The Wassermann test was negative. An electrocardiogram indicated extreme myocardial damage.

At autopsy every tissue except the cardiac valves, eyes and nails was found to be involved in metastatic pigmented tumors. Particularly massive nodules were found in the medullae of the suprarenal glands, in the hypophysis apparently involving both lobes and the intermediary portion, and in the posterior portion of the thalamus just beneath the corpus callosum.

This case is reported because of the speed and tremendous extent of the metastases, and because no primary focus could be demonstrated. In view of the extensive involvement of both suprarenal glands and the malignant appearance of the medulla of one of them it is thought that the primary melanoma probably originated in one of these glands.

A LARGE GALLSTONE EXTRUDED AT THE UMBILICUS. ELLIS KELLERT.

A married woman, 60 years old, entered the clinic and stated that two years previously she began to experience attacks of gastric distress and vomiting. These symptoms continued at irregular intervals, usually weeks apart. The bowels were regular and the feces were normal in color. Recently the periods of distress had been more frequent and were associated with severe pain in the upper right quadrant of the abdomen. She entered the hospital during one of these attacks. There was severe epigastric pain radiating to the right lower quadrant of the abdomen, with a rapid pulse and fever.

The patient appeared slightly jaundiced, and a nonfluctuating mass 12 by 15 cm. in size was found in the right upper quadrant of the abdomen. The leukocyte count was 17,600 per cubic millimeter, and the polymorphonuclear leukocytes were 78 per cent. Other laboratory tests were negative. A roentgenogram disclosed

obstruction in the first portion of the duodenum. After several days the patient felt more comfortable and left the hospital.

On her recent visit to the clinic she directed attention to a small, black, hard area involving the umbilicus. This object proved to be a calculus, which was readily extracted by means of a thumb forceps. After removal of the calculus yellow bile discharged from the opening, and a sinus tract to the region of the gallbladder was probed.

The calculus was somewhat oval in outline and measured 4.5 by 3.5 by 3.5 cm. All surfaces were encrusted with brownish-black, glistening, amorphous material which separated readily on handling. When the calculus was sectioned, the cut surface had a distinctly concentric lamellated character, many yellow and dark brown layers being present. On microscopic examination there was an abundance of cholesterol mingled with bile pigment. No bacteria were found.

ENDOSALPINGIOSIS OF THE BLADDER. G. H. KLINCK JR.

A white woman, 40 years of age, complained of irregular attacks of pain in the right lower quadrant of the abdomen, associated with frequency of micturition, burning and pain. She had had menorrhagia and metrorrhagia for two months and had lost some weight. Endometrial curettings showed tuberculous endometritis. Cystoscopy revealed a globular tumor, 3 cm. in diameter, with a wide base, in the right wall of the bladder about 3 cm. to the right of and above the right ureteral orifice. A minute bit of this tumor showed bladder epithelium only, and a report of benign papilloma was made.

Complete hysterectomy was done, at which time it was noted that the right tube was so firmly adherent to the right posterolateral wall of the bladder, just opposite to the tumor, that it was necessary to cut the tube away from the wall of the bladder. Examination showed tuberculous endometritis and myometritis with a few early tubercles in the adhesions between the right tube and the bladder. The wall of the right tube in the region of the adhesions to the bladder contained numerous glands composed of columnar epithelium surrounded by a small amount of loose stroma. No blood was found in these glands, although many were dilated. Convalescence was uneventful.

The patient returned six weeks later, and the growth in the bladder was removed through a suprapubic cystotomy. The surface was congested and soft, with small cystlike spaces just beneath the surface. Section showed a growth radiating from the wall of the bladder. It had a soft, edematous stroma containing many small cystic spaces toward the periphery. Microscopically the tumor was composed of dilated glands lined by flat to columnar epithelium. The glands contained amorphous granular material but no intact red cells. In the peripheral portions of the tumor there was very little stroma. Toward the base the glands became smaller, the epithelium more columnar and surrounded by dense fibrous stroma. Gland structures could be traced from the base through the wall of the bladder and well into the old scar tissue, the site of the previous salpingectomy. The surface of the mass was covered over by a layer of hyperplastic bladder epithelium. The patient made an uneventful recovery.

This case illustrates another complication of tubal adhesions in which the tubal mucosa invades another organ. Sampson described such lesions in the ovary and uterus, and in this instance the urinary bladder was involved. Endometrial tissue is able to invade these organs in much the same way.

EFFECT OF CESIUM CHLORIDE OF TRANSPLANTED TUMORS OF MICE. ARTHUR W. WRIGHT and CLARENCE F. GRAHAM.

A full report of these studies appeared in the *American Journal of Pathology* (9:789, 1933).

NEURO-EPITHELIOMA OF THE RETINA. J. SCHLEIFSTEIN.

In 1891 Flexner described a tumor of the retina of a type which has since been known as neuro-epithelioma. The case which I present is a typical instance of neuro-epithelioma according to the classic description recorded by Flexner. The parents of a girl 6 months old consulted a physician because they had noticed something the matter with her eye for the last two months. A diagnosis of glioma was made and the eyeball enucleated.

The specimen consisted of an eyeball somewhat larger than normal for the age. The cornea appeared dull. Section through the eye showed a soft, grayish-pink tumor almost completely filling the eyeball.

Microscopic examination showed a compact mass containing sheaths of round cells with deeply staining nuclei and very little cytoplasm. Many mitotic figures were present. Very little fibrous stroma could be observed. Numerous foci of hemorrhage and necrosis were seen. Scattered throughout the tumor were many rosette formations, which were demonstrated particularly well with Mallory's phosphotungstic acid-hematoxylin stain.

ADENOMA OF THE SWEAT GLANDS. J. SCHLEIFSTEIN.

Adenoma of the sweat glands forms an interesting class of tumors, some of which border on malignancy. The case to be reported appears to belong to the latter group.

A young man, 23 years of age, complained of a lump behind the occiput. The attending physician made a clinical diagnosis of epidermal cyst and removed the mass, which proved to be a small tumor the size of a lima bean. It contained numerous papillary projections. Microscopic examination showed an actively growing sweat gland adenoma malignum of low grade.

CARCINOMA OF THE ISLETS OF LANGERHANS. V. C. JACOBSEN.

A white American pharmacist, 36 years of age, suffered gastro-intestinal upsets between 1927 and 1930. These were characterized mainly by diarrhea. In 1930 a diagnosis of faulty fat metabolism was made, and the patient was given a diet high in carbohydrate and low in fat. The symptoms continued and in 1932 a diagnosis of diabetes mellitus was made on the basis of glycosuria. He was put on a diabetic regimen and shortly afterward suffered insulin shock with the blood sugar below 25 mg. per hundred cubic centimeters. Roentgen examination suggested a tumor of the head of the pancreas. Operation was not advised.

The patient required constantly increasing amounts of sugar in order to ward off insulin shock. By August, 1933, he required a glass of orange juice every three hours day and night. In the latter part of August he could not be aroused three hours after taking nourishment but regained consciousness after 2 glasses of orange juice, which he required thereafter every two hours. Insulin shock developed suddenly, with the blood sugar 39 mg. per hundred cubic centimeters. Roentgen examination verified the suspicion of a large tumor in the region of the head of the pancreas, and an exploratory laparotomy was done.

The tumor was roughly the size of a small grapefruit and inoperable, but a small bit was removed for biopsy. The liver contained several small nodules of firm white neoplastic tissue. One of these was removed. During the operation the patient received 150 mg. of dextrose intravenously. The blood sugar rose to 527 mg. per hundred cubic centimeters and within nine hours dropped to 93 mg. Thirty-two hundred milligram-hours of radium was applied over the epigastrium.

Following operation it was possible to prevent insulin shock by the administration of 50 Gm. of dextrose every four hours day and night. At present the patient is in fairly good health and has no symptoms so long as the dextrose is taken regularly. He has slight secondary anemia.

Pathologic examination of the tissue removed from the region of the main pancreatic tumor showed narrow cords of epithelial cells slightly squamous in type,

infiltrating fat and connective tissues. No mitoses were seen. The nodules in the liver were very cellular epithelial growths, the cells showing much regularity and no mitoses. Often arranged in large alveoli with a few capillaries in and about them, they bore a striking resemblance to pancreatic islets. Bensley stains showed only beta granules present.

NOTE.—This patient died Dec. 24, 1933, from hemorrhage caused by erosion of the second portion of the duodenum by the carcinoma in the head of the pancreas. The body and tail showed parenchymal atrophy with persistence of islets. Metastases were present in the liver only. Much glycogen was found in the kidneys. The hyperinsulinism was under good control, the blood sugar post mortem being 180 mg. per hundred cubic centimeters. The case will be reported in more detail by Dr. Nelson K. Fromm.

EXTREME HEMOLYSIS ASSOCIATED WITH MARKED LIVIDITY AND HEMOGLOBINURIA. J. J. CLEMMER.

An unmarried white woman, aged 30, was admitted to the hospital in a conscious but toxic state. About thirty-six hours previously she had had an abortion. Her chief complaints were pain in the lower part of the abdomen, nausea and numbness of the legs. She had a moderate fever, a rapid pulse with low blood pressure, and a rapid respiratory rate. The uterus was enlarged and soft, and the cervix was dilated. A profuse black bloody vaginal discharge was present. The entire body was a diffuse dusky red. Catheterization of the bladder yielded an ounce (30 cc.) of dark red fluid, which microscopically showed only a few crenated erythrocytes. The urine contained large quantities of hemoglobin. Blood withdrawn for typing was markedly hemolyzed. Thirteen hours after admission, following a brief convulsion, the patient expired.

Postmortem examination revealed a generalized infection with Clostridium Welchii, with the genital tract the probable portal of entry.

The uterus was enlarged and soft. The wall of the fundus was lacerated. A small probe could be passed through it at one point. A few bits of placental tissue were present in the cavity. The entire genital tract was acutely inflamed.

Striking evidence of generalized hemolysis was present. The serous linings were stained uniformly pink. The endothelial lining of the heart and large vessels showed similar staining. The kidneys were intensely deep red.

There was no evidence of gas production in the tissues at the time of necropsy. However, a few days later, bubbles of gas were found situated deeply in some of the organs which had been saved as gross specimens.

This case is presented to emphasize the marked hemolytic action exhibited by some strains of Cl. Welchii. This organism has been known to produce a hemolysin, but the biologic activity usually stressed is its production of gas in vivo and in vitro. Clinically, gas production was not demonstrable in this case. However, the marked hemolysis observed both ante mortem and post mortem was sufficient to suggest the diagnosis of Cl. Welchii septicemia.

MEASLES ENCEPHALOMYELITIS. R. J. LEBOWICH.

Five days after the appearance of the rash, this nervous complication of measles developed suddenly in a white child, 4 years of age, with convulsions and muscular twitchings limited at first to the left side of the face, later spreading to the neck and right arm. The child became unconscious, failed to answer questions, and was not responsive to external stimuli. The eyes were drawn to the left. No attempt was made to move the left arm or leg. The spinal fluid was normal. The patient became progressively worse with increasing frequency of muscular spasms over the right and then the left side of the body. Death occurred about forty-eight hours after the initial development of the convulsions.

To the naked eye the only changes of note in the brain were pronounced congestion and edema of the leptomeninges. Microscopically, however, these tissues

showed a slight, intermittent perivascular infiltration by lymphocytes, plasma cells and macrophages. Focal histologic changes were also distributed rather uniformly from the frontal cortex into the upper cervical cord. These changes consisted of perivascular and marginal zones of demyelinization and complete destruction of axis-cylinders located almost always about the small veins. They were of the sharply punched-out type and formed wide sleeves about the vessels for long distances, with extensions along their branches.

The most common cell present in the extra-adventitial infiltrates was the lymphocyte. Plasma cells were common. Frequent active or inactive macrophages associated with occasional polymorphonuclears were also observed, especially in the very severe perivascular lesions. Many astrocytes were present either within the extra-adventitial lesions or at the periphery, often flowing out into the more intact nerve tissue. In general, the ganglion cells were remarkably well preserved and complete necrosis was rare. There were no signs of neuronophagia.

It is of interest to note that in the centrum ovale minute irregular masses of lime salts were occasionally observed in the ground substance, especially in areas of incomplete disintegration. No calcification of the arteries of the type now familiar in chronic epidemic encephalitis was seen.

NEW YORK PATHOLOGICAL SOCIETY AND NEW YORK ACADEMY OF MEDICINE, SECTION OF SURGERY

Joint Meeting, Nov. 23, 1933

PAUL KLEMPERER, *President*

SYMPOSIUM ON GASTRIC NEOPLASMS

SOME FEATURES OF THE PATHOLOGY OF PRIMARY CANCER OF THE STOMACH. ARTHUR PURDY STOUT.

The malignant neoplasms of the stomach include both carcinomas and sarcomas, the latter forming about 3 per cent of the total number. The vast majority of the carcinomas arise from the mucosal lining or gland cells and have a tendency to form glands and to secrete mucin. The growth tends to advance centrifugally from the focus of origin, i. e., into the lumen and into and along the wall of the stomach. But different cancers display these tendencies in differing degrees, and this fact enables one to divide them roughly into two great groups: (*a*) the *fungating*, with growth chiefly into the lumen, and (*b*) the *infiltrating*, with growth chiefly along the wall paralleling the lumen or into the wall away from the lumen. These two groups can be subdivided, depending on the presence or the absence of ulceration.

The fungating group includes about one third of the carcinomas and contains most of the better differentiated, less malignant tumors, which can be successfully resected.

The infiltrating group comprises about two thirds of the carcinomas and contains most of the poorly differentiated, very malignant tumors.

The presence of metastases in the regional lymph nodes is a prognostic sign of the gravest significance no matter what the type of tumor, but an enlarged, hard lymph node does not always contain metastases.

Carcinomas develop at the margins of simple gastric ulcers; a cancer may occur in a stomach which has a simple ulcer in a different part of it. An infiltrating ulcerated carcinoma may simulate a simple ulcer.

The duodenum is seldom invaded by a gastric cancer, and when it is, the invasion is of microscopic extent. However, a portion of a fungating tumor may protrude through the pylorus and stick out into the duodenum.

DISCUSSION

N. C. FOOT: As Dr. Stout says, carcinoma of the stomach might be classified on a histologic or histogenetic basis, this being qualified by various subheadings depending on whether mucus is formed, whether fibrous tissue reacts to the presence of the tumor and similar factors. Unless the surgeon knows the characteristics of each type of carcinoma he can gain little knowledge as to prognosis from the histogenetic diagnosis alone. Dr. Stout's simple classification of carcinoma into tumors that grow outward or fungate and those that grow inward or infiltrate gives one an idea of the gross appearance of the type and an inkling as to the prognosis. Coupled with the prognosis, as based on fungating or infiltrating growth, is Dr. Stout's warning as to the importance of microscopic examination of the regional lymph nodes. Only the microscope can indicate whether there is or is not metastasis to the lymph nodes, and the statement that enlarged nodes do not necessarily contain metastases is borne out by my experience. The converse is equally true: small and apparently innocent nodes may contain small metastases that will develop into dangerous carcinomas. This makes microscopic examination of all nodes removed at operation imperative.

The fact that fungating tumors are less malignant than infiltrating ones goes hand in hand with their differing degrees of differentiation and specialization; those that are forming glands and differentiating toward their normal goal do not tend so much to invade, while those that form distorted travesties of glands, or mere plugs or masses, or even mere gangs of discrete cells, are very poorly differentiated and therefore know no laws and proceed to invade foreign territory without providing themselves with passports. The grading of tumors is based on the degrees of differentiation, so that tumors of the lower grades of malignancy fall automatically into Dr. Stout's outgrowing group, while those of the higher grades come into the ingrowing, or infiltrating, group.

I am not much impressed with the importance of grading tumors, for two reasons. The first one is that one tumor may show areas of differing degrees of malignancy, so that several slides from the same growth may be classified in as many grades. Secondly, the criteria for grading are largely matters of personal impression and individual judgment. If the surgeon is familiar with the criteria employed by his favorite pathologist, grading may mean something to him, but if he takes the grades of a man with whom he is not well acquainted he may easily be misled. Few pathologists take the time to count the well and the poorly differentiated cells in a given tumor. They usually grade a tumor by superficial impression, which makes the whole thing a personal matter. Is it not better plainly to state one's opinion as to whether a growth is markedly, moderately or slightly malignant in its microscopic appearance, and let it go at that?

Dr. Stout has come out courageously for the possibility of a cancer developing in a chronic ulcer, and I am very glad that he has done so. Last year I had a patient who had had a chronic ulcer for about six years; when he was subjected to operation, the microscope revealed a tiny carcinoma developing in the margin of the ulcer, which on gross inspection looked like an ordinary chronic ulcer. It would have been missed if radial sections of the crater and lip, like slices of a pie, had not been made. The simultaneous development of an ulcer and a cancer in the same stomach has been observed by many.

The freedom of the duodenum from carcinoma is indeed baffling; the duodenum and the pylorus are so essentially alike in histologic structure that it seems strange that the one should go almost scot-free while the other constitutes the site of predilection for gastric carcinoma—this in spite of the fact that chronic ulcers occur in each. Boyd mentions this immunity in his textbook and cites Deaver's figures, which show that when carcinoma occurs in the duodenum it is usually found in the second portion near the papilla of Vater, while the first and third segments rank next, in that order. Ewing's figures show that duodenal carcinoma forms 4 per cent of all intestinal cancers.

As to gastric sarcoma, occasionally one meets with a leiomyosarcoma of the stomach that simulates carcinoma clinically, but gives practically no symptoms except hematemesis until it is too late to do anything surgically. It usually occupies the fundus, causes no change in the secretions, is not palpable until it has metastasized, and does not show on roentgen examination. It causes widespread metastasis in the liver and elsewhere, does not invade the nerves, and grows much more slowly than does a carcinoma. Hence the clinical history does not feature pain. The patient outlives his predicted span of life on account of the slow progression of the tumor, and one must be very cautious in giving a prognosis as to time in such cases, after operation has revealed extensive involvement of the liver. I have seen two such tumors in the past decade; both ran a slow and comparatively symptomless course; both occurred at the fundus; both were diagnosed as chronic ulcer, and both progressed slowly to an ultimately fatal outcome. The diagnosis of leiomyosarcoma under the microscope is not easy, for there are other sarcomas that may be confused with it; some of these may be so very embryonal that a recognition of the type cell is well nigh impossible, but this is of interest chiefly to the pathologist; the manifest malignancy of the tumor is not difficult to recognize, and this is the all-important fact in the eyes of the physician and the surgeon.

ARTHUR PURDY STOUT: Dr. Foot mentioned the variations in differentiation that many carcinomas of the stomach show. That is certainly true in my experience. They are not all of one type; they vary, many of them in different parts, and when I have found that, I have formulated the conception that a tumor is as malignant as its most malignant-appearing part; usually a tumor which has some part of it poorly differentiated belongs to the more malignant group.

ROENTGEN ASPECTS. ROSS GOLDEN.

Malignant disease of the stomach lends itself to detection by roentgen methods by virtue of its three inherent characteristics, namely, its ability to produce tumor masses that project into the lumen and result in "filling defects," its power to infiltrate the walls, change their contour and interfere with their movements, and its tendency to ulcerate. Dr. Stout described the fungating type, in which the formation of tumor masses predominates, and the infiltrating type, in which the formation of tumor masses may be slight or absent. A tumor that does not infiltrate is benign, e. g., mucous polyps, which are recognized by absence of stiffening of the wall and interference with peristalsis. The lantern slides shown illustrate some of the roentgen manifestations of gastric neoplasms, some of the difficulties in their detection and some problems in differential diagnosis.

In one instance, an extensive infiltrating carcinoma failed to keep the stomach from contracting and expelling large masses of barium because the malignant cells infiltrated between and did not destroy the muscle bundles.

An annular ulcerating carcinoma of the prepyloric region was accompanied by a peptic ulcer a little higher up. The malignant growth bulged through the pylorus into one side of the duodenal bulb.

Peptic ulcers in general differ from ulcerating malignant neoplasms by the fact that their craters are usually smaller and relatively deep, while those of carcinomas are larger, shallow and saucer-like. Peptic ulcers occur on or near the lesser curvature, while malignant growths may occur anywhere. Sometimes on careful palpation irregularities around the margin of the malignant crater or a too extensive stiffening of the wall may be demonstrated. Holmes and Hampton (*J. A. M. A.* **99**:905, 1932) have found all ulcerating lesions in the prepyloric region to be malignant. A peptic ulcer should be definitely smaller after three weeks of an adequate dietary regimen. Cases illustrating these points and exceptions to the rule are shown: A patient had an ulcer of the lesser curvature in 1924 which disappeared, an ulcer of the duodenum and of the lesser curvature in 1926 which disappeared, another in 1929 which disappeared, and an ulcerating carcinoma in 1933. An ulcer of the lesser curvature which did not reduce in size under treatment had the histologic characteristics of a malignant growth on

one side of the crater and of peptic ulcer on the other. An ulcer immediately adjacent to the pylorus showed no histologic evidence of malignancy. A large, deep ulcer of the lesser curvature, measuring 5 cm., in a man 75 years old, disappeared in two months; the man was alive nine years later.

The diagnostic differentiation of hypertrophy of the pyloric muscle from early annular carcinoma of the prepyloric region in an adult may be impossible roentgenologically and may be difficult at operation (illustrations given). The impression on the proximal end of the duodenal bulb described by Kirklin and Harris (*Am. J. Roentgenol.* **29**:437, 1933) as characteristic of a hypertrophied muscle may be absent, and a similar impression may be produced by the bulging of a carcinoma through the pylorus.

A carcinoma of the cardiac end of the stomach may be extremely difficult to detect. The importance of examination of the patient in the supine position with rotation from side to side was emphasized.

In three instances, a sarcoma of the stomach produced a round, sharply defined filling defect in which was the shadow of a barium-filled crater.

Syphilis of the stomach is a rare condition which cannot be differentiated from carcinoma by roentgen methods. Lymphoblastoma of the stomach may be differentiated only when two levels in the gastro-intestinal tract are involved. Tuberculosis of the stomach has been reported as simulating carcinoma (Renander: *Acta radiol.* **11**:636, 1930).

In conclusion it may be said that the diagnosis of *early* carcinoma of the stomach is extremely difficult and is necessarily attended with certain risks. The roentgenologist will probably make some false positive interpretations. The surgeon will have to explore on relatively meager roentgen evidence of malignancy and will probably do some resections of benign growths because he could not be sure that they were not malignant. However, by intimate correlation of the efforts of the roentgenologist, the surgeon and the pathologist, the goal may be approached, which is the accurate diagnosis of early carcinoma of the stomach.

DISCUSSION

W. H. STEWART: Dr. Golden's statement that to date he has not been able to confirm Dr. Kirklin's opinion that a cup-shaped concave base to the duodenal bulb, with or without an apparent widening of the pyloric canal, indicates hypertrophy has been my experience. My last venture in the realms of pyloric hypertrophy proved disastrous, for the patient had a carcinoma. However, it must be admitted that thickening of the pylorus is a true identity and should give distinct roentgen signs. It is up to roentgenologists to recognize them. The difficulty will be to differentiate hypertrophy from malignancy.

I agree that most of the lesions in the prepyloric region are malignant. Again my experience coincides with Dr. Golden's, for every once in a while I come in contact with a nonmalignant lesion within the limits defined by Holmes and Hampton.

Spasm in any part of the intestinal tract is the most disturbing factor encountered and the most difficult to differentiate. Repeated examinations are often an aid, as the permanency of the defective filling is thereby directly tested. Spasm may be persistent enough to give the same deformity in filling at several examinations, and this is especially true of spasm on the gastric side of the pylorus.

In a large experience covering a long period of years I have always considered an ulcer of unusual size as "malignant until proved otherwise." Only in very exceptional cases has this rule proved wrong.

Cancer of the body of the stomach is very insidious, in many instances being inoperable when discovered.

Dr. Golden has so thoroughly covered the roentgenologic aspects of carcinoma in the lower third of the stomach that I thought it might be of interest to discuss some of the roentgen signs of cancer at the cardia. I have enumerated ten roentgen points as indicating a malignant growth in the upper end of the stomach.

It is recognized that many of these can be produced by conditions other than cancer, but if they are grouped, it is extremely probable that they will indicate whether or not the condition is malignant. The ten roentgen signs of involvement of the cardiac end of the stomach by cancer are:

1. A dilatation of the lower part of the esophagus
2. Any abnormal retention of barium in the lower part of the esophagus
3. Barium passing through the esophageal orifice in a continuous stream
4. A narrowed esophagus and an unchanging canalization through the tumor
5. A frozen mass, the infiltration preventing the normal movements of the lower part of the esophagus
6. A mass visible in a gas bubble
7. A mass visible after the first swallow of barium, with a distorted rugal pattern; a mass visible after distention of the stomach by the full meal—a contracted lumen
8. Barium forking over the mass
9. Gastric hypermotility
10. Esophageal antiperistalsis

These ten signs must be correlated with a clinical history of dysphagia, loss of weight and of appetite, regurgitation of mucus, vomiting of blood, or other positive findings.

Many patients with gastric cancer appear for diagnosis with the lesion too far advanced for surgical resection; one of the great fields for future progress in medical diagnosis is in the earlier recognition of cancer. The physician must be more ready to suspect cancer and at an earlier date. He must insist that every laboratory procedure possible be used in studying the case. To wait for the advanced typical picture of cancer is to wait too long. Before cancer of the stomach can be diagnosed early the physician must insist that roentgen examinations be made as regularly as urinalyses and repeated as often as examinations of the sputum.

The symptoms of cancer of the cardiac end of the stomach may be very indefinite even up to death. One of my patients had no complaint other than that of vomiting blood; another had only tarry stools for two weeks.

Dysphagia when present is of great value; it is found in more than half the cases. The patient may not volunteer information as to this, but answers affirmatively when directly questioned. When difficulty in swallowing or substernal pain is complained of, cancer of the cardia should be borne in mind and excluded only after thorough examination.

A cancer of the cardia involving the esophageal sphincter secondarily or by direct extension is much easier to detect roentgenographically than an involvement limited to the posterior wall. It is in this type of lesion that cancerous involvement is missed until it is so extensive that the diagnosis is obvious.

OPERATIVE INDICATIONS AND PROGNOSIS IN CASES OF NEOPLASM OF THE STOMACH. FORDYCE B. ST. JOHN.

I have reviewed 718 cases of carcinoma of the stomach in patients admitted to the Presbyterian Hospital, New York, in the past twenty-five years, 1908 to 1932, inclusive.

In 430 of the 718 cases an exploration was made, and in 86 per cent of these a pathologic specimen was obtained. In 212 cases, or 29.6 per cent, operation was not advised, because of advanced disease. Fifty-seven patients, or 7.9 per cent, refused operation. In 10 cases, or 1.4 per cent, the clinical diagnosis was made only at postmortem examination.

In 98 of the 430 cases explored, resection of the tumor was carried out. In other words, resection was reasonable and possible in 1 of 4.5 cases in which an

exploration was made, and in 1 of 7 cases observed in the clinic. The postoperative mortality has been steadily reduced during the twenty-five years; in the last five years it was 25 per cent.

Results in 98 Cases in Which Resection Was Performed

Patients who died		69
Death from postoperative complications	33	
Death from delayed postoperative complications	1*	
Deaths at eighteen and forty-six months from pneumonia and cerebral accident, respectively, with no signs of recurrence	2	
Deaths from recurrence	33	
Living patients		26
Living (from four to twenty-one months), with lymph node involvement and showing signs of recurrence	4	
Living (from eight to thirty-eight months) with lymph node involvement but showing no signs of recurrence	3	
Living (from eight to forty-eight months), without lymph node involvement and showing no signs of recurrence	10	
Living and apparently well (of 36 patients followed five years or more)	10	
Living and apparently well (of 20 patients followed ten years or more)	7	
Patients not followed		3

* This patient died, two months after discharge, from peritonitis secondary to perforated jejunal ulcers. Autopsy showed no metastases or recurrence of the primary growth.

It was found from the study that the greatest factor in longevity when radical surgery was possible was the pathologic characteristic of the tumor referred to by Stout as the fungating type.

DISCUSSION

ALLEN O. WHIPPLE: There are two points I should like to emphasize: One is the great advantage that has been found, at least in this study, in the combined efforts of the pathologist, the roentgenologist and the surgeon. I know of no more interesting subject for investigation than this group of 98 cases of stomachs resected for carcinoma. This combined pathologic, roentgenologic and clinical study indicates the type of work that is being done in clinics throughout the country.

The other point which I wish to emphasize is that the surviving patients with arrests of cancer of the stomach should be shown at least once a year in these hospital clinicopathologic conferences. One of the reasons why the impression that carcinoma of the stomach is malignant is so prevalent is that the subject is discussed at clinicopathologic conferences and very little elsewhere. The impression of the medical student, the intern and the younger clinician is largely based on cases shown at the clinicopathologic conference, and I know of nothing more healthy, from the standpoint of calling the attention of the younger clinicians to carcinoma of the stomach, than the presentation of late results, the five and ten year arrests, not only of cancer of the stomach but of other types. If that were done once a year, at least, at the clinicopathologic conference it would have a healthy and sane influence on hospital organization.

FREDERIC W. BANCROFT: I am going to confine my discussion to Dr. St. John's paper. I think it is an interesting and in many ways encouraging account of a discouraging subject. Last year, at the meeting of the American Surgical Association, Maes of New Orleans read a paper on the tragedy of gastric cancer. His report was most discouraging as a study of end-results. I think Dr. St. John has shown in this same year definite steps in progress.

I should first like to emphasize the honesty of the statistics, and particularly the statement that the deaths that have occurred while the patients were in the hospital, whether or not these deaths were due to this disease, have been reported. This has not been done in certain published compilations of statistics of operative results in the clinics of the country. I think the improvement in results which is shown by Dr. St. John to have taken place since July 1933 is astonish-

ing. It shows the value of statistics. There are many factors which may have helped to bring about this improvement. It is undoubtedly due in part to a trained group of men. It may be due in part to the use of spinal anesthesia. It may be due to the use of the Levin tube. It may be due to the efforts to prevent depletion of body fluids, and there may be other causes which have influenced the statistics. Also it occurred to me that a decade ago there was a greater number of deaths from pneumonia. I wonder whether there were deaths due to pneumonia following spinal anesthesia in the series of a decade ago as well as deaths due to inhalation anesthesia. In the statistics of the hospital with which I am associated spinal anesthesias give a higher percentage of pneumonias than any other type.

Two things are worth emphasizing in this problem of cancer of the stomach, and they also hold in cancer elsewhere. The first is preventive surgery. Surgeons have come to depend on the roentgenologist for a great deal of diagnosis and prognosis in cases involving the stomach. Perhaps they depend too much on him and do not analyze sufficiently the clinical symptoms and the general course of the disease. As long as he has them dependent on him, I think there is something else for him to do. The American Society for the Prevention of Cancer and the periodic health magazines are constantly emphasizing the necessity for periodic health examinations. A great many people come to physicians to be assured that they have not cancer. I do not think that physicians can assure those patients that they have or have not an early malignant process in the gastro-intestinal tract without some roentgenographic evidence but, at present, if a physician sends such a patient to a roentgenologist and he charges the current prices for a gastro-intestinal series, the cost of the ordinary periodic health examination becomes prohibitive. Therefore I think the roentgenologists will have to meet the physicians and say that they will give a certain type of service in periodic health examinations—for instance, a few gastric plates and one or two barium enemas—at a minimum rate. If there is a suspicion of a pathologic process there is no reason then why they should not increase the cost to the patient. I cannot see how, by doing a digital, a rectal and possibly a proctoscopic examination, with palpation of the abdomen, a physician can assure a patient that he has or has not cancer of the stomach or colon. I feel definitely sure that since physicians have adopted periodic health examinations they must carry them out and carry them out thoroughly.

The second thing which seems to me important is: What should be one's concept of a suspicious case? If the mortality following operations on gastric ulcers is considerable, and the benefit derived is the discovery of an occasional carcinoma, it seems to me one has to divide the cases into two types: (1) those of duodenal ulcer and (2) those of ulcer of the lesser curvature, which Dr. Cole and Dr. Lahey have shown will in the great majority of cases subside under rest in bed and medical therapy. Dr. Lahey has made the rule that even if there is no evidence of tumor after three weeks the patient must be sent for at the end of eight weeks and reexamined. If there is any small nicking or scar where the ulcer was the case warrants a surgical exploration. Certainly one's first concept is that rest in bed will decrease the size of the ulcer.

One then comes to the prepyloric ulcers. I am more and more convinced that if the prepyloric ulcer does not show definite roentgenologic and clinical evidence of improvement in a relatively short time the patient should be operated on. I think if one tried to follow some such concept, one might have some means of improving the five and ten year results.

LEOPOLD JACHES: I agree that early diagnosis is desirable. I must say, however, that early diagnosis is difficult if, by early carcinoma of the stomach, is meant a very small lesion which one can perhaps palpate when one has the stomach between one's fingers at the operating table and which can be diagnosed only when the pathologist has made a microscopic examination. There is perhaps one phenomenon that might help, and this Dr. Golden has referred to, namely, rigidity of the gastric wall about the area of the lesion.

When one comes to differentiate between ulcer and carcinoma, I might give another rule which is just as good as Dr. Golden's and, by the same token, does not always hold; it is that generally a carcinoma will be found in older persons and a benign lesion in younger ones. Nevertheless, Dr. Golden has shown you a film relating to a patient of over 70 who had what Dr. Golden chose to call typical evidence of carcinoma, which clinically, at least, does not seem to be that. On the other hand, once in a while one finds a very young person, even a person in the twenties, with a carcinoma of the stomach. It seems to me, therefore, that it is more important for the roentgenologist to localize the lesion than to make a positive diagnosis of a malignant or a non-malignant process. That, in the final analysis, is left to the pathologist. The size of the lesion should be an indication for the clinical procedure, whether operative or medical.

As to the disappearance of ulcers, in my experience that is a delusion and a snare. Quite a few times I have seen an ulcer demonstrated, the patient treated, and the ulcer disappear. The patient feels better. After a while he commences to have symptoms, perhaps hematemesis; he is reexamined by the same roentgenologist, and no ulcer is seen. One waits a little while. The patient does not improve and is again examined by the roentgenologist, and there is no ulcer, while clinically the case is becoming more and more desperate. The surgeon operates and finds the ulcer which was seen at the first examination, and it is practically of the same size and shape. That has happened more than once.

With regard to the differentiation of carcinoma from syphilis of the stomach, there is no typical appearance of syphilis of the stomach. The few syphilitic stomachs that I have seen have had the tumors on the greater curvature, but I doubt whether this may be considered a pathognomonic sign. The fact that a patient has had syphilis, or even the fact that he has a four plus Wassermann reaction at the time of the examination, does not mean that the defect in the gastric shadow is a gumma and not malignant.

I should like to confirm Dr. Stewart's observation that a carcinoma high up in the stomach is much more difficult to diagnose than one lower down.

In closing, I should like to take issue with Dr. Bancroft on the question of the cost or, rather, on his suggestion that the roentgenologist take just one plate "and that may be enough." Yes, that would be enough if the patient had a huge carcinoma that could be palpated through the abdomen, but if the lesion is very early, which is the one he is trying to discover by these periodic health examinations, fluoroscopy and only one plate will never help. That one plate will miss it in nine cases out of ten. I have repeatedly seen instances in which, with a series of films, the lesion was discovered on only one, and on repeated examinations the same thing happened; and although when fluoroscoping my associates and I knew what to look for, we did not find it on the fluoroscope, and the lesion which was later proved by operation to have been present showed on only one plate of a series. How is the roentgenologist or anybody else to know which one of the films is going to show the lesion?

Ross Golden: I did not feel that the time allotted me and the nature of the program justified a detailed discussion of roentgenologic technic. The technical points brought out by Dr. Stewart and Dr. Jaches are well taken. I may say, however, that I feel that fluoroscopy is essential, and that the patient should be examined not only upright but prone and supine and turned freely from side to side. I do not see how that can be done on films alone, and I say that without meaning to minimize the importance of films. The patient should also be examined and palpated not only when the stomach is full but when only one or two swallows of barium are trickling down. After the best positions to show the lesion have been determined fluoroscopically, the evidence can be confirmed on the films. I cannot emphasize too much that I think careful fluoroscopy is of vital importance.

I wish to thank Dr. Stewart for his ten points; many of them make the diagnosis absolutely, and others, I feel, will be present also in other conditions.

FORDYCE B. ST. JOHN: The point which Dr. Bancroft makes is important, namely, the preoperative care, including maintenance of fluid balance, rest, repeated lavage, etc. So far as postoperative pulmonary complications are concerned, I feel that no form of anesthesia can eliminate these. In my hands spinal anesthesia (*p*-n-butylaminobenzoyl *di*methylamino-ethanol hydrochloride) is the most satisfactory.

NEW YORK PATHOLOGICAL SOCIETY

PAUL KLEMPERER, *President*

Anniversary Meeting, Jan. 25, 1934

CONGENITAL NEPHRITIS: SUBACUTE GLOMERULONEPHRITIS AND CARDIAC HYPERTROPHY IN AN INFANT 4 MONTHS OLD. CHESTER R. BROWN.

On postmortem examination of a syphilitic infant 4 months old there were found contracted kidneys with finely granular surfaces and a hypertrophied heart weighing 43 Gm. Microscopy revealed subacute glomerulonephritis.

The patient was admitted to the hospital with a diagnosis of bronchopneumonia and died nine days later. The Wassermann reactions of the mother and the child were strongly positive. Neither had received antisyphilitic treatment. The delivery and pregnancy were normal.

The essential anatomic findings were as follows: The body was that of an undernourished, underweight white female child. A bloody nasal discharge was present. The heart showed marked hypertrophy, especially of the left ventricle; it weighed 43 Gm. Both kidneys were greatly enlarged, the right weighing 43 Gm. The cortex was finely granular. Punctate hemorrhages were numerous. The spleen and liver were enlarged and congested. The anatomic diagnosis was: subacute glomerulonephritis; cardiac hypertrophy; interstitial fibrosis of the lungs; chronic passive congestion of the viscera, and congenital syphilis.

Microscopic Examination.—All the renal glomeruli were involved but varied in size and in stage of inflammation. About 75 per cent were enlarged; the remainder were smaller and partially or completely atrophied. Bloodlessness of the loops was characteristic, although there were many old and recent capsular hemorrhages. An increase in the number of endothelial cells was present in some glomeruli; the cells of others had degenerated. Fibroblastic adhesions of the tuft and capsule, older and recent "crescents" and partial or complete hyalinization were present in various glomeruli. Some presented fibrous constricting periglomerulitis. Many glomeruli had disappeared. The cortical architecture was disorganized. Some tubules presented marked dilatation with epithelial fatty degeneration; many were atrophic or compressed by interstitial fibrous tissue; others showed marked regeneration of the epithelium. Numerous red cells and hyaline and granular casts filled the lumens. Small cortical scars were present, which caused focal cortical granulations. In all the vessels the media was markedly hypertrophic. In the arterioles intimal hyperplasia was marked. Necrotizing arteriolitis was present. The veins were tremendously thickened. Plasma cell infiltrations were not present, and lymphocytic foci were minimal.

In the heart, the muscle bundles were widely separated by interstitial edema, a moderately cellular connective tissue and a great number of newly formed, congested capillaries. Many of the latter had ruptured. The muscle nuclei were enlarged and stained deeply. In the larger coronary arteries and veins the media was greatly thickened. In their smaller branches intimal hyperplasia was present. All were surrounded by extensive adventitial fibrosis.

The walls of the pulmonary alveoli were moderately thickened, the capillaries were congested, and there was an increase of fibrous tissue. The lining endo-

thelial cells were increased in number, enlarged and pyknotic. Some were desquamated and contained pigment granules. The vessels were all greatly thickened with marked adventitial fibrosis. Bronchopneumonia was present.

The fibrous trabeculae of the liver and spleen were increased throughout both organs. The hepatic sinuses were congested. Erythroblastosis was absent.

In the vessels of all the viscera the media was markedly thickened .

Levaditi stains on all tissues were negative.

The microscopic diagnosis was: congenital subacute glomerulonephritis; hypertrophy of the heart; diffuse interstitial myofibrosis.

Comment.—The lesions in the kidney suggest that the nephritis was of longer duration than the extra-uterine life of the infant. The cardiac hypertrophy suggests that hypertension was present. Nephritis of this degree with cardiac hypertrophy has been reported in a nonsyphilitic baby 4 weeks old (Ashby). Acute diffuse glomerulonephritis has been reported (Karsner) in a full-term nonsyphilitic infant, dead fifteen minutes after birth. The fetal kidney is extremely susceptible to various toxins circulating in the maternal blood. Maternal infections, drugs and abortifacients may cause nephritis. The criteria for microscopic diagnosis of congenital syphilis vary with different authors. Lymphocytic and plasma cell infiltrations, interstitial and perivascular, are stressed by some. Others emphasize endarteritis obliterans. Only the latter was significant in this kidney. Spirochetes *per se* are probably not the direct etiologic agents in glomerulonephritis of the syphilitic new-born. The syphilitic kidney is particularly susceptible to bacterial toxins arising in the gastro-intestinal tract, which are the direct cause of the nephritis.

DISCUSSION

LOUIS GROSS: When one examines the coronary arteries of an adult with hypertension one finds it very difficult to determine how much of the intimal lesion is due to the hypertension and how much to the changes belonging to the age. After the first decade, or at times even before the end of the first decade, some coronary vessels may show changes which resemble in their extent those found in vessels of much older persons. Dr. Brown's case is a very fortunate one from this point of view; here is an infant 4 months old in whom the intima was undoubtedly a simple structure. Whatever changes may have taken place, one may reasonably assume that they were due to the hypertension that must have been present, as evidenced by the thickness of the myocardium. Just what did the intima of the coronary arteries look like?

PAUL KLEMPERER: It is not safe to determine the duration of nephritis from the histologic appearance. Sometimes nephritis may proceed very rapidly, and a picture which it is customary to correlate with a few months may obtain within a shorter period. I wonder, therefore, whether one can definitely say that this is a case of congenital nephritis. Four months is, after all, a period the changes of which in an adult correspond with the picture that is seen here. The changes might proceed much more rapidly in the infant, and the same picture might be produced in a shorter time.

CHESTER R. BROWN: In the smaller coronary vessels and in some of the larger ones the intima was hyperplastic.

It is true that this advanced nephritis might be produced by a glomerular inflammatory process originating after the birth of the infant.

AN ATYPICAL CASE OF MULTIPLE MYELOMA. SHELDON A. JACOBSON and MARTIN G. VORHAUS (by invitation).

The case presented seems to be of interest from both a theoretical and a practical point of view. A. R., 42 years old, was first admitted to the hospital on June 20, 1932. She had been under intermittent treatment in the clinic of the hospital for four years with symptoms involving almost every system of her body. For some time during this and subsequent stays in the hospital the same confusing

multiplicity of symptoms continued. With time, however, the following signs and symptoms assumed particular prominence both to the clinician observing her and in view of subsequent observations at autopsy.

There was marked, general, progressive muscular weakness. General pain was complained of (the lower part of the back being most troublesome), and gastrointestinal distress made its appearance. The musculature and subcutaneous tissues were of a putty-like consistency. Translucent, waxy papillomas appeared on the eyelids, lips, buccal mucosae and anus. The vertebrae and the sternum were sensitive to palpation. Between 6 and 8 Gm. of Bence-Jones protein was eliminated daily. There was moderate anemia. The white blood count varied between 11,500 and 20,600; the differential count was normal. (A few days before death the white blood count reached 27,900). Repeated careful roentgen examinations of the skeleton revealed no abdominal conditions.

The diagnosis was held to lie between multiple myeloma and idiopathic amyloidosis.

At autopsy removal and sagittal section of the vertebral column and careful examination revealed nothing noteworthy in the gross. The marrow of the ribs, on the other hand, was suspiciously pale and gelatinous. The musculature of the back had completely lost its normal color, being deep yellow. The tongue was enlarged. Microscopic section showed myeloma cells infiltrating all parts of the spongiosa of all vertebrae and ribs examined. An amyloid-like substance was present in the lungs, liver, spleen, stomach, intestines, tongue, bladder, uterus, fallopian tubes, lymph nodes and skin. Chemical examination of the muscles failed to reveal appreciable quantities of amyloid.

The chemical derangements which characterized the local and general metabolic processes of this patient would no doubt shed much light on the nature of myeloma, could they be properly interpreted. That is beyond our power at present. Of immediate practical importance is this new demonstration of the insufficiently appreciated fact that a pronounced myelomatous involvement may fail to give roentgenologic evidence of its existence. Even a careful gross examination of affected bone may mislead a pathologist into excluding a myeloma which is actually present. Doubt is thrown, therefore, on the existence of the so-called one-bone myeloma and on the existence of essential amyloidosis with Bence-Jones proteinuria.

DISCUSSION

JACOB FURTH: Since tumors were absent, and the disease process was diffuse and not "multiple," would you not prefer designating the condition as myelomatosis? What are, in your opinion, the cells that infiltrated the bone marrow?

MENDEL JACOBI: I should like to ask Dr. Jacobson whether or not there was any evidence of cellular necrosis in the many slides which he unquestionably studied, and then I should like to say a word about giant cells in amyloidosis, a subject which Dr. Jacobson brought up. Experimentally my associates and I have found (and we have been working experimentally with amyloidosis for a considerable period of time) that in the very earlier stages of amyloidosis, when it is intracellular rather than extracellular, there is often a giant cell reaction. As the extracellular amyloid becomes manifest and increases in amount there occur simultaneously necrobiotic changes in the giant cells, so that in places we can no longer distinguish the cell outlines; the further the process progresses, the fewer are the intact giant cells and the more numerous are the fragmented giant cells and giant cell nuclei present in the amyloid masses. Finally, as the amyloid replaces large areas of parenchyma, all evidences of cellular reactivity vanish. These changes my collaborators and I have described in detail in a recent number of the ARCHIVES (**17**:50, 1934).

I should like to ask whether there was any amyloid in the kidney. I presume there was not. It is interesting that in the larger number of patients with Bence-Jones albuminuria amyloid is not found in the kidney. The Bence-Jones protein

may be the matrix of the amyloid, and it is likely that its secretion and excretion through the kidneys do not permit a deposition of amyloid in this organ.

PAUL KLEMPERER: I am not quite clear on the diagnosis of myeloma in this case. I feel rather disinclined to believe in the so-called diffuse myeloma. But, granted that such an entity exists, there is one question I should like to ask: What are these cells which Dr. Jacobson calls myeloma cells? Rustitzky, in his definition, maintained that the hyperplastic nodules in the bone marrow consist of nothing else than what is found in the bone marrow. If these cells are not bone marrow cells, what are they? Dr. Jacobson mentioned extramedullary myeloma without involvement of bone. I do not understand what this is. I think one might not be too strict and too orthodox if one believes that a myeloma must be absolutely limited to the bone. A myeloma without skeletal involvement I cannot understand. I might have misunderstood Dr. Jacobson, but I think he mentioned cases in which "myeloma cells" were found without skeletal involvement.

In regard to the question of the lymphocytic origin, I might also have misunderstood Dr. Jacobson when he said that his concept contradicts that of the lymphogenic nature of the myeloma cells. I think there are cases of myeloma on record in which myelocytes were found. The myeloma cell, or the cell which composes the nodules in the bone, need not be of lymphocytic origin. I do believe the cell in the so-called plasma cell myeloma is not a true plasma cell, but an atypical lymphoblast or, better, a hemocytoblast. While it is probable that the greater number of myelomas do not consist of mature and typical bone marrow cells, there are certainly some which do consist of them. It is true that one cannot always identify the cells of a myeloma with a definite, mature bone marrow cell, but one can compare them with the ancestral cell of the bone marrow cell. I should like to know what Dr. Jacobson calls myeloma cells, and what is the difference between his concept and the classic concept of myeloma.

SHELDON A. JACOBSON: The question of the origin of myeloma cells is a pitfall for the feet of the unwary, and I have great hesitation in speaking of that and in defining a myeloma. Since, however, I am forced to answer that question, I should say that my diagnosis of a myeloma, at least of an intraskeletal myeloma, for the moment, is based on the presence of a tumor mass within the bone or soft tissue, composed preferably of cells of the type that are called plasma cells—like marrow cells, large cells with abundant cytoplasm and eccentric nuclei, containing chromatin divided up into many little points. I have made the diagnosis in this case on that basis. That was the preponderant cell type in the smear which I made of this marrow; it was a cell not native to the bone marrow. It did not belong to the red cell series or to the myelocytic series. It was not a reticulum cell. It did not belong to the lymphocyte cells. It had the closest identity with the sort of cell that is found in some atypical cases of myeloma in which one finds nodules of soft tissue in great numbers growing in and destroying the bone marrow. Such tumors may be accompanied by Bence-Jones proteinuria. That is the best definition I can give.

The origin of the cells is not yet settled, and I hardly care to make a statement. I think that the best discussion is that of Wallgren, who relates the primitive cells in some way with the myeloid series. I think they are stem marrow cells which have not yet differentiated.

Cases have been reported in which the tumors did not involve the skeleton at any point. There was a case of a large tumor of the nasopharynx which was made up of just the cells which I have described, such a growth as one is accustomed to call plasma cell myeloma. It was associated with amyloidosis and Bence-Jones proteinuria. If these tumors can grow outside the skeleton and arise in lymphoid tissue, as this nasopharyngeal one is reported to have done, the myeloma cell must be a cell that is somtimes, at least, derived from lymphoblastic tissue. Dr. Klemperer throws doubt on the freedom of the skeleton from myeloma in such cases. In agreement with him, I point out that mine is a case which on microscopic examination showed a predominant cell type which one calls the myeloma

cell, but which had, nevertheless, nothing to be seen on macroscopic examination. How much more difficult it is, therefore, to rule out the presence of a skeletal myeloma when one has a more limited autopsy, and sometimes not an autopsy, but just a roentgen study! I think I have answered the first speaker as well as I can.

In reply to Dr. Jacobi, I wish to say that I did not observe any necrosis in this tumor. The predominant feature was degeneration. Giant cells were rare, though well defined. I saw no signs of giant cells fading out or merging into the amloid which surrounded them. In all of them the nuclei were perfectly dark. It is my impression that most of the cells had nuclei which were likewise dark and well defined.

STRUCTURE OF THE NORMAL CALVARIUM IN DIFFERENT AGE GROUPS. SIDNEY A. BERNSTEIN (by invitation).

A detailed microscopic examination was made of calvaria ranging from that of a 7 months premature infant to that of a man aged 82 years. These were arbitrarily divided into four groups:

Group 1, those up to 1 year of age, representing the infantile calvarium.

Group 2, those from 1 to 20 years of age, representing the period of greatest growth.

Group 3, those from 20 to 50 years of age, in which the greatest change in the internal architecture was taking place.

Group 4, those from 50 to 80 years of age, presenting senile changes.

The infantile calvarium (thickness of 0.8 mm.) presents no division into two compact tables with a spongiosa between. Instead the bone is arranged in overlapping sheets, like shingles, composed of (1) immature intramembranous bone, which is formed at the suture, and (2) a somewhat riper bone, the result of pericranial apposition. The former type diminishes on receding from the suture. The preformed connective tissue becomes incorporated in the premature bone as long Sharpey fibers. Growth takes place at the suture in a manner analogous to that at the epiphysis of a long bone; that is, the connective tissue proliferates at the center, while becoming ossified at the margins of the suture. Four important growth changes are taking place: (1) The skull is enlarging in its transverse plane; (2) it is enlarging in its vertical plane; (3) it is getting thicker; (4) not only the skull as a whole, but each element of it, is moving in a vertical direction.

The skulls in group 2 have a thickness of from 1 to 6.5 mm. A differentiation has taken place into tabula externa, diploe and tabula interna. The compact tables consist of bone laid down by the dura and pericranium, which is lamellated horizontally. Early this apposition takes place without interruption; therefore no cement lines are present, but after from five to seven years this process slows down and cement lines appear. At this time, also, the older and more centrally placed bone begins to undergo creeping resorption, and haversian systems make their appearance. The tabula externa and the tabula interna are similar in structure, except that the former is thicker and the change is more advanced. The cellular lymphoid marrow of the diploic spaces begins to show islands of fatty marrow.

Group 3 have a thickness of from 5 to 8 mm. Haversian systems are present in all layers of the compacta. This remodeling may be so far advanced, especially in the tabula externa, as to wipe out even the last vestiges of the original horizontal lamellated bone. Owing to resorption on the pericranial surface of the tabula externa and apposition of bone on its endosteal surface, this table may move centripetally or, more rarely, the changes may be reversed and the table move centrifugally.

Group 4 have a thickness approximately the same as in the foregoing period. The diploe encroaches on both compact tables as the result of the resorption of bone on their endosteal surfaces. These tables are now thin and porosed. The diploic spaces are large and the trabeculae thin with little knobs of localized

apposition of bone here and there. Rests of horizontally lamellated bone are found deep in the diploic trabeculae as proof that these occupy a niveau which was formerly part of the compact table. The bone cells of the older bones die off and show absence of nuclear staining.

DISCUSSION

ALFRED PLAUT: Up to the age of about 8 years the dura mater at the convexity is firmly adherent, as it is at the base throughout life. After that age the dura mater is separated from the bone at the convexity. What is the histologic basis of this difference?

DAVID P. SEECOF: May I add that in senility the dura again becomes adherent to the under surface of the bone. Why?

I think this is a remarkable paper. There is need of more studies of this kind. I should like to ask how many cases there were in each group, in order that one may have an idea of how far the normal variations have been covered.

I should like to ask whether concomitant with the changes in the bone there were changes in the blood supply. That is important in relation to the changes that occur in bones in diseased states, such as osteomyelitis. I think from what I can gather that there must be changes in the blood supply, especially in the venous supply to the diploe.

H. L. JAFFE: Dr. Bernstein carried out these interesting studies in Vienna, in Erdheim's laboratory, when he was a fellow from the Hospital for Joint Diseases.

One is prone to consider the calvarium as something that has to be got out of the way in approaching the cranial cavity. After it is removed it is usually casually examined, then put down and forgotten. The calvarium, if it is studied, presents tremendous normal variation. I had occasion to find out something about the normal calvarium. I wanted to make a comparative study of the normal calvarium in connection with some calvaria which I was studying. When I looked into what was known about the normal and the pathologic anatomy of the calvarium I found a large hiatus in the literature. There was considerable information on the embryologic development of the skull, especially the calvarium. There was a good deal of information on suture closure and suture function. The anthropologic aspects of the skull and the comparative anatomic details were well known. But when I came to getting practical information on how thick the calvarium is in a man 60 years of age I found that search of the literature was of little avail. Furthermore, it is difficult to learn exactly the measurements of the outer and inner tables and of the diploic zone. Dr. Bernstein has done much to fill in the gap in the information. He cautiously states that all the skulls that he studied were so-called normal skulls, and he said that they were so-called normal because there was no cranial disease. Not infrequently one comes across a heavy, sclerotic skull in a very old person. There is really little information as to why skulls sclerose with advancing age. In connection with senility, Dr. Bernstein states that eccentric atrophy may come with advancing age. This, the symmetrical osteoporosis of old age, leads to erosion of the outer table in the parietal region. With more knowledge of the normal, it would be simpler to understand the basis for the thickening of the skull in Paget's disease and the details of the changes in other fibrotic diseases.

SIDNEY A. BERNSTEIN: In answer to Dr. Plaut's question regarding the separation of the dura, I think the matter depends on whether bone is being apposed or resorbed on the surface. When it is being apposed, a thick cambium layer is present and adherent. The fibers of the periosteum are being incorporated in the newly formed bone as Sharpey's fibers. As a result, the dura is adherent to the bone and is separated with difficulty. But when resorption of bone is taking place, the Sharpey fibers together with the surrounding bone disappear, and thus the connection between the periosteum and the bone is loosened.

The question was raised, Why should the dura be adherent in advanced age? In many of my calvaria of about the age of 40 to 50, especially toward the

parietal region, I found a different type of bone, which I did not mention for lack of time. This bone was laid down on the outer surface of the tabula externa in a very thick layer, was very primitive, taking on an extremely dark blue staining reaction, and consisted of confluent calcareous granules. Over this bone was a very thick layer of osteoid tissue, and running through both these layers from the periosteum were many Sharpey's fibers. This may explain the renewed adherence of the periosteum to the bone at a time when the rule otherwise is bone resorption on the surface.

As to Dr. Seecof's question concerning the number of cases in each group, I made it a point to take at least three cases from each decade, so when the group, e. g., group 3, encompasses three decades, nine calvaria were studied. From each skull cap three sections were taken from a wedge beginning at one side of the sagittal suture and extending across the midline to the opposite temporal region, including the suture between the temporal and parietal bones.

As regards changes in the blood supply, both in the diploic spaces and in the compact tables, I found much more vascularity in the younger age groups. In the very young the compacta contained many Volkmann's canals, especially the tabula interna. As mentioned, the contents of the diploic spaces changed with oncoming age from a vascular marrow to a cellular marrow and finally to a fatty marrow. It may be that this decrease in blood supply is the cause of the frequent occurrence of dead cells in aged skulls. Bone cells were found in which the nuclei took no stain, and this not only in the horizontal lamellated bone, but also in the older haversian systems. I say "older" because one can fairly accurately judge how old they are by the difference in the staining reaction; the bone in the older haversian systems takes a more basophilic stain than does that in the younger ones.

PERIARTERITIS NODOSA (NECROTIZING ARTERITIS), WITH A NOTE ON ABDOMINAL RHEUMATISM. CHARLES K. FRIEBERG (by invitation) and LOUIS GROSS.

In the last two years at Mount Sinai Hospital there have been eight patients with necrotizing inflammatory arterial lesions (periarteritis nodosa) whose condition was found at autopsy. Of these, four had unquestionable rheumatic heart disease, including Aschoff bodies in the myocardium. Strict criteria were employed for both the diagnosis of rheumatic heart disease and that of periarteritis nodosa. The clinical basis for the diagnosis of rheumatic heart disease consisted of acute polyarthritis with fever, pericarditis and signs of valvular disease. Pathologically there were characteristic deformities of the valves, auricular lesions, pericarditis and Aschoff bodies in the myocardium in each case. The diagnosis of periarteritis nodosa was not based merely on isolated instances of necrotizing arteritis in single organs. The lesions were very extensive, involving at least the heart and the kidney in each case and generally numerous other organs as well. The lesions were grossly visible either as markedly thickened vessels or as characteristic nodules along the course of the blood vessels. Thromboses, infarctions and aneurysms were present. Microscopically there were panarteritis with necrosis of the arterial wall, periarterial inflammation, thickening of the intima, narrowing of the lumen and occasionally evidences of healing.

Furthermore, the lesions were severe enough to give rise to clinical symptoms. Orchitis was present in both the males. Abdominal pain was present in all four patients, and in two was sufficiently severe to lead to operative intervention. Symptoms of renal involvement were present in all. Had we been less strict in our criteria of heart disease or of periarteritis nodosa, we should have had a considerable number of additional cases available besides the four of combined rheumatic heart disease and periarteritis nodosa which we present. (The case reports with slides were presented.)

A relationship between periarteritis nodosa and rheumatic fever has been repeatedly conjectured. We do not believe that the association has ever been conclusively demonstrated. The relationship has been suggested by certain similarities

in clinical features, by the suggested allergic nature of the diseases and by occasional instances of arthritis in patients with periarteritis nodosa. However, in the latter instances only rarely has mention been made of the finding of endocarditis at autopsy and never have Aschoff bodies been described in these cases.

Further evidence for the relationship under discussion has been found in the vascular lesions described in rheumatic fever. Aschoff, Geipel and Coombs described necrotizing inflammatory lesions in the finer branches of the coronary arteries in rheumatic heart disease. Klotz described vascular lesions in rheumatism which were examples rather of productive than of destructive inflammation. Watjen described a panarteritis with destructive changes involving the smaller coronary branches. In all of these cases, however, the pathologic alterations were present only in the heart or in the heart and aorta. More significant is the report of Von Glahn and Pappenheimer who found vascular lesions with necrosis and inflammation involving many organs in ten of forty-seven cases of rheumatic heart disease. However, these lesions were present in only one or two organs in any given case. They were found only on microscopic examination. They apparently did not give rise to clinical symptoms. Thromboses, aneurysms and infarctions were not present. The authors themselves believed that there were clearcut differences between these lesions and those of periarteritis nodosa.

In the cases which we have described not only was there an undoubted association of rheumatic heart disease and periarteritis nodosa at postmortem examination, but also in the clinical course of the disease in three of the four cases the symptoms generally ascribed to rheumatic fever were present simultaneously with those generally ascribed to periarteritis nodosa. We therefore suggest that the vascular lesions termed "periarteritis nodosa" may be caused, among other conditions, by rheumatic fever. Furthermore, it is suggested that in cases of acute rheumatic fever with severe abdominal symptoms sometimes leading to exploratory operations, an organic basis for the symptoms may be found in the vascular lesions of periarteritis nodosa.

DISCUSSION

C. J. Sutro: As subcutaneous nodules are present both in rheumatic fever and in periarteritis nodosa, the presence of both types in one case would be most unusual. Were there any subcutaneous nodules in these four cases? If there were, were they removed, and if so, what did they show?

Irving Graef: Two cases bearing on this subject have been studied recently at Bellevue Hospital. They raised the question, certainly in my own mind, as to the possible identity of the lesions in the blood vessels with those of the rheumatic pattern. One was that of a man, 65 years of age, who had inactive rheumatic heart disease and who died in heart failure with severe mitral stenosis and auricular thrombosis. Clinically several lesions were noted beneath the skin on his back and once on his left arm; they had a dusky blue tinge and disappeared. They were thought to be subcutaneous nodules, but on removing one of them a lesion characteristic of periarteritis nodosa was found. At necropsy four more lesions were found, one along the aorta, one in the bladder and one in each kidney. As I said before, the heart was entirely negative for *active* rheumatic carditis. The man died of heart failure, and whatever factor produces periarteritis nodosa produced these lesions.

The second case was that of a 15 year old boy who had an acute respiratory infection with an exanthem, and died in uremic coma with convulsions three weeks later. He was in the hospital only twenty-four hours, so the clinical data are inadequate. At autopsy he had widespread necrotizing arteritis with almost universal involvement of the renal arterioles—arteriolitis. There was an acute necrotizing nonbacterial valvulitis (with no gross lesions on the valves) and no Aschoff bodies in the myocardium. This case I think belongs to the same group as Lamb's case described in 1912-1913.

I believe the lesions in periarteritis nodosa are certainly distinct, and in many cases can be sharply separated histologically from the lesions of the blood vessels

in rheumatic carditis, as one sees them in the common run of cases, but I am not sure that even an identical appearance points to an identical etiology, even when rheumatic carditis is present.

The wide base from which necrotizing arterial lesions can spring seems to be widening every year. I need only recall the case reported by Dr. Helpern and Dr. Trubek of a person with gonococcal endocarditis in the right side of the heart, sepsis, and necrosing arteritis systemically distributed. Similar lesions have been reported in other acute infections (I have seen them associated with pneumococcic infections), tropical diseases like yellow fever, typhoid and so on.

CHARLES K. FRIEDBERG: Cases in which subcutaneous nodules are found are always very helpful when they appear clinically. In none of these cases were such nodules discovered. Of course, as I have pointed out, the diagnosis of periarteritis nodosa has sometimes been made when they were not present.

In regard to Dr. Graef's interesting cases, I think that the evidence for the etiologic relationship between the vascular lesions which we observed and the rheumatic fever is not based only on the high incidence of rheumatic fever in our series of cases of periarteritis nodosa. In certain of the cases the period of the symptoms was very brief, and some of the symptoms were definitely those of rheumatic fever, and others, such as orchitis, were definitely those associated with periarteritis nodosa. Furthermore, there were evidences of nephritis and uremia, which are so uncommon in uncomplicated rheumatic fever (Baehr and Schiffrin) that we can hardly believe them to have been a part of the rheumatic fever except so far as rheumatic fever and periarteritis nodosa are part of one and the same complex. Abdominal pain is a more frequent, though not common, symptom of rheumatic fever, but then again abdominal pain is one of the triad of symptoms which appear so commonly in periarteritis nodosa that I feel one is not going very far afield in concluding that in these cases rheumatic fever was a definite etiologic factor in the arterial lesions. I should like to add that we have had other patients with histories of rheumatic fever, evidences of valvular lesions and thrombo-endocarditis of the valves without Aschoff bodies whom we have not included in the series but whose condition may very well be part of a general rheumatic infection.

LOUIS GROSS: I should like to say a few words in regard to Dr. Graef's remarks. I should like to turn the tables around and say that I am not convinced that these two cases are not cases of rheumatic fever, but it was just because we had this doubt in our mind that we leaned over backward and included those cases which gave us only convincing evidence, namely, the Aschoff bodies. We do not want to leave the impression in the mind of any one that we consider periarteritis nodosa as perhaps largely occurring in rheumatic fever. Undoubtedly there are a great many cases of periarteritis nodosa in which rheumatic fever is not associated, and there are many diseases causing cardiac lesions, but we want to point out that among the diseases in which both conditions occur, rheumatic fever is one.

Book Reviews

The Lyophilic Colloids (Their Theory and Practice). By Martin H. Fischer, Professor of Physiology, the University of Cincinnati, and Marian O. Hooker, Research Associate in Physiology, the University of Cincinnati. Price, $4.50. Pp. 250, with 84 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1934.

This book presents a summary of the work of Fischer's laboratory during the past fifteen years. It is divided into three parts. The first part records in detail certain experiments which illustrate the general nature of the lyophilic (hydrophilic) colloids. The second part deals with chemical applications, and the third with biologic applications. The physician and physiologist will be interested primarily in the third part.

The authors point out that when certain colloid systems are cooled, for example, phenol/water, quinoline/water, soap/water, gelatin/water and casein/water, the nature of the solution gradually changes from one of X-in-solvent to one of solvent-in-X, with many intermediate types of solutions, all of which have different chemical and physical properties. Experiments are recorded in detail which show how these properties are affected by the addition of various substances. Particular attention is paid to the effect of acids and alkalis on the hydration capacity of the solid phases of such systems. The theme is essentially that the properties of protoplasm resemble more closely those of that phase of a colloid system in which water is dissolved in X than those of the phase in which X is dissolved in water. The laws of the dilute solution apply to the second type of solution, but not to the first. The authors believe that many erroneous deductions have been made as a result of trying to apply these laws to protoplasm. According to them, this concept explains why "no physical chemist has ever found any direct or simple relation between any one of the properties of the dilute solution phase of a lyophilic colloid system (its p_H, its osmotic concentration or its electrical properties) and the 'behavior' of the total system." Their disagreement is chiefly with the physical chemist. In their opinion, he degrades the cell to a drop of water in which various salts and nonelectrolytes are dissolved. He relegates the proteins to a third place and mentions the fats and carbohydrates as an afterthought. "To get a 'behavior' out of" the mixture "at all comparable with that of a living cell" he surrounds it with a "membrane," the properties of which are said to vary in different types of cells. "The colloid chemist" [Fischer] "thinks most of these things wrong. . . . He begins by wiping out the cell 'membrane' of the physical chemist because entirely hypothetical. With the pure chemists, he places the proteins of the living mass first. He mentions next the salts, but not as things which are merely mixed into the protein but as materials which, as acids or bases, were originally united with the protein. Third, he puts the water, but not as a solvent for the protein-salt complex but as a material dissolved in the latter. This membraneless hydrated protein-salt compound is the unit of his living mass. Into it (for the present) he merely mixes (emulsifies) the fats and the higher carbohydrates which are found in cells." The authors state that there are difficulties in the osmotic concept of the cell. On the biologic side, they claim that "an osmotically constructed living cell is an impossibility." On the physicochemical side, they state that the so-called "quantitative" experiments failed. They claim that the exchange of water between cells and their environment depends on the hydration capacity of colloids, which in turn is affected by various substances, notably acids and alkalis. The pressure theory of edema "breaks of its own weight," and edema becomes a "problem in colloid chemistry. . . . We have to look to changes in the tissues and cells themselves for the first 'causes' of an edema."

The book contains much repetition, but may be read with profit by all those interested in biology and physiology, particularly those who are interested in the exchange of water between cells and their environment. The experiments on various colloid systems are of interest, but the interpretation of various biologic phenomena by analogy from them has been carried too far. While the hydration capacity of colloids may play a rôle in the exchange which occurs between cells and their environment, the authors' attempt to establish it as the only factor will meet with opposition. Physical chemists will find it difficult to believe that they have satisfactorily excluded osmosis and that pressure has been adequately disposed of as a factor in cardiac edema. Many chemists will question the authors' theme, namely, that protoplasm is a solution of water-in-X. Nevertheless, the book stimulates thought about fundamental biologic problems and, is therefore, a valuable contribution to physiology.

Books Received

La syphilis expérimentale. Etude critique et nouvelles recherches. P. Gastinel, Professor agrégé, and R. Pulvénis, Chef de Laboratoire, à la Faculté de Médecine de Paris. Price, 45 francs. Pp. 244, with 19 figures and 4 plates. Paris: Masson et Cie, 1934.

This is a critical review of the work on experimental syphilis with results of new investigations. The first chapter traces the early stages in the study of experimental syphilis in man and animals. Then come chapters on: experimental syphilis in apes, monkeys, the rabbit, and other animals; on the routes of generalization, the infectiousness of the lesions, and of the different organs; on experimental syphilis in general and the factors that may modify its evolution; on unapparent experimental syphilis; on immunity in experimental syphilis, and on the reaction of Meinecke in syphilitic rabbits. The monograph will be of much interest and value to all who are concerned in the study of experimental syphilis.

Journal of Technical Methods and Bulletin of the International Association of Medical Museums No. XIII. Maude E. Abbott, M.D., editor. Price, $2.00. Pp. 204. Montreal (3640 University Street): International Association of Medical Museums, 1934.

This number contains: a sketch of D. S. Lamb (1843-1929) of the Army Medical Museum in Washington; editorials on various topics; articles on museum administration, museum and autopsy technic, photographic methods, microscopic technic, teratology, cardiovascular anomalies and endometrial hyperplasia; book reviews; obituaries of international members; proceedings of the association, the constitution, and a list of the members.

Brucella Infections in Animals and Man. Methods of Laboratory Diagnosis. I. Forest Huddleson, Department of Bacteriology and Hygiene, Michigan State College. Price, $2.25. Pp. 125, illustrated. New York: Commonwealth Fund, 1934.

Die pathologisch-anatomischen Grundlagen der Chirurgie des Rektumkarzinoms. Von Priv.-Doz. Dr. Heinrich Westhues, Erster Oberarzt der chirurgischen Universitäts-Klinik Erlangen. Mit einem Geleitwort von Prof. Dr. Schmieden, Frankfurt a.M. Price, 29.50 marks. Pp. 113, mit 107 zum teil farbigen abbildungen. Leipzig: Georg Thieme, 1934.